EPREX

Epoeitin alfa

COMPOSITION

Epoeitinum alfa ..... 40,000 IU or 336 microgram per ml

PHARMACEUTICAL FORM

Epoeitinum alfa is a sterille, clear, colourless, buffered parenteral solution for intravenous or subcutaneous injection.

PHARMACOLOGICAL PROPERTIES

Epoetinum alfa is a purified glycoprotein hormone that stimulates erytropoiesis. Epoetinum alfa is produced from mammalian cells into which the gene coding for human erythropoietin has been inserted.

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

Pharmacodynamic properties

ATC Code : B03XA01

Erytropoeitin is a mitosis-stimulating factor and diferentiating hormone which stimulates erytropoiesis. Epoetinum alfa cannot be distinguished from human erytropoietin with regards to its biological properties.

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

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

Pharmacodynamic responses to HSA-free Epoetinum alfa, change in percent reticulocytes, haemoglobin, 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 40,000 IU/ml SC once weekly).

Change in percent reticulocytes, haemoglobin, and total red blood cell counts, as well as, respective AUCs of these pharmacodynamic parameters, were similar between two dosing regimens of HSA-containing Epoeitinum alfa (150 IU/kg SC three times per week and 40,000 IU/ml SC once weekly) in both healthy and anemic cancer subjects. Increases in AUC of haemoglobin and RBC count were lower in anemic cancer subjects than in healthy subjects.

The effect of Epoetinum alfa on energy level and ability to conduct daily activities has been studied in multi-center double-blind, placebo-controlled clinical trials and two open-label trials of anaemic cancer patients receiving chemotherapy. In a large double-blind trial, patients treated with Epoetinum alfa compared to patients treated with placebo experienced significant improvements in energy, daily activity level and fatigue. Smaller randomized and open-label studies have supported these improvements in quality of life parameters that were noted to accompany increases in haemoglobin as small as 1 g/dl.

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

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

In a randomized controlled study EPO-INT-76 (referred to as the 'BEST' study) with Epoetinum alfa in 939 women with metastatic breast cancer receiving chemotherapy, patients received either weekly Epoetinum alfa or placebo for up to a year. This study was designed to show that survival was superior when an ESA was administered to prevent anaemia (maintain haemoglobin levels between 12 and 14 g/dL or hematocrit between 36% and 42%). The study was terminated prematurely when interim results demonstrated that at higher mortality at 4 months (8.7% vs 3.4%) and a higher rate of fatal thrombotic events (1.1% Epoetinum alfa vs. 0.2% placebo) in the first 4 months of the study were observed among patients treated with Epoeitinum alfa. Investigator-attributed cause of death within the first 4 months was most commonly disease progression: 28 of the 41 deaths in the Epoetinum arm and 13 of 16 deaths in the placebo arm. Investigator assessed time to tumor progrresion was not different between the two groups. Based on Kaplan-Meier estimates, at the time of study termination, the 12-month survival was lower in the Epoeitinum alfa group than in the placebo group (70% vs 76%), HR 1.37, (95% CI 1.07, 1.76) p=0.012.

In another placebo-controlled study using epoetin beta in 351 patients with head and neck cancer (reffered to as the ENHANCE study), study drug was administered to maintain the haemoglobin levels of 14 g/dl.in women and 15 g/dl in men. Locoregional progression-free survival was significantly shorter in patients receiving epoetin beta.

In the DAHANCA 10 study 522 patients with primary squamous cell head and neck cancer receiving radiation therapy were randomized to darbepoietin alfa or placebo to maintain a haemoglobin level greater than 12 g/dl. An interim analysis in 484 patients demonstrated a 10% increase in locoregional failure rate among darbepoietin alfa-treated patiens. At the time of study termination, there was a trend toward worse survival in the darbepoietin alfa treated arm.

A systemic review of 57 randomized controlled trials (including the BEST and ENHANCE studies) evaluating 9353 patients with cancer compared ESAs plus transfusion with transfusion alone for prophylaxis or treatment of anaemia in cancer patients with or without concurrent antineoplastic therapy. An increase relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 patients) was observed in ESA-treated patients. An overall survival hazard ratio of 1.08 (95% CI. 0.99, 1.18; 42 trials and 8167 patients) was observed in ESA-treated patients. Use of ESAs for treatment of anaemia in cancer patients on chemotherapy was associated with an over all survival odds ratio of 0.99 (95% CI: 0.72, 1.36). Sub-group analysis of anaemic cancer patients receiving chemotherapy from this systemic review demonstrates an odds ratio of 0.92 (95% CI: 0,78, 1.09) for platinum based chemotherapy and 1.10 (95% CI: 0.96, 1.24) for chemotherapy without platinum.

Pharmacokinetic properties

Subcutaneous administration

Serum concentrations following subcutaneous injection are lower than those following intravenous injection. Serum levels increase slowly and reach a peak 12 to 18 hours after subcutaneous dosing. The peak serum concentration is below the peak observed using the intravenous route (approximately 1/20th of the value).

There is no accumulation: serum levels remain the same, wether 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 healty 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 Epoteinum alfa in healthy subject, the following parameters were estimated using data corrected for preclose endogenous erytropoeitin 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 Epoetinum 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 Epoetinum alfa in healthy subjects, the following parameters were estimated using data corrected for predose endogenous erythropoietin concentration during Week 4:

	Cmax (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 Epoetinum alfa after a dose of 120 IU/kg is much lower than that of the intravenous drug: approximately 20%.

Pharmacokinetic parameter 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 Epoetinum 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 (m/l/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 (17.6)	35.3 (15.8) (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 it as indicated unless specifically stated
b C_{min} was estimated by everaging weekly predose serum concentrations during the study

Pharmacokinetics of HSA-free Epoetinum 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 Epoitenum 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} (mIU/ml)	C_{min}[b] (mIU/ml)	t_{max} (h)	$t_{1/2}$ (h)	CL/F (m/l/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)[a]	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-PO1-108

a n as indicated unless specifically stated

b C_{min} was estimated by averaging weekly predose serum concentrations during the study

Preclinical Safety Data

Chronic Toxicity

In some pre-clinical toxicological studies in dogs and rats, but not in monkeys, Epoitenum alfa therapy was associated with subclinical bone marrow fibrosis. Bone marrow fibrosis is a known complication of chronic renal failure in humans; it may be related to secondary hyperparathyroidism or unknown factors. In one study, there was no difference in the incidence of bone marrow fibrosis in haemodialysis patients treated with Epoitenum alfa for 3 years and haemodialysis patients not treated with Epoetinum alfa.

Carcinogenicity

Long-term carcinogenicity studies have not been carried out. There are conflicting reports in the literature regarding ESAs as tumour proliferators. The clinical significance of these reports, based on *in vitro* findings from human tumour samples, are unknown.

Mutagenicity

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

Reproduction 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 Epoetinum 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 the 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 fetuses of the 500 IU/kg/day group. There were no Epoetinum alfa-related effects on the F_2 generation fetuses.

CLINICAL PARTICULARS

Therapeutic Indications

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

POSOLOGY AND METHOD OF ADMINISTRATION

Method of administration

The subcutaneous route of administration should be used.

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

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

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 injection should be given in the limbs or the anterior abdominal wall.

Cancer Patients

Adult cancer patients:

The subcutaneous route of administration should be used.

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

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

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

Alternatively, Epoetinum alfa 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/µl above baseline] the dose should remain unchanged.

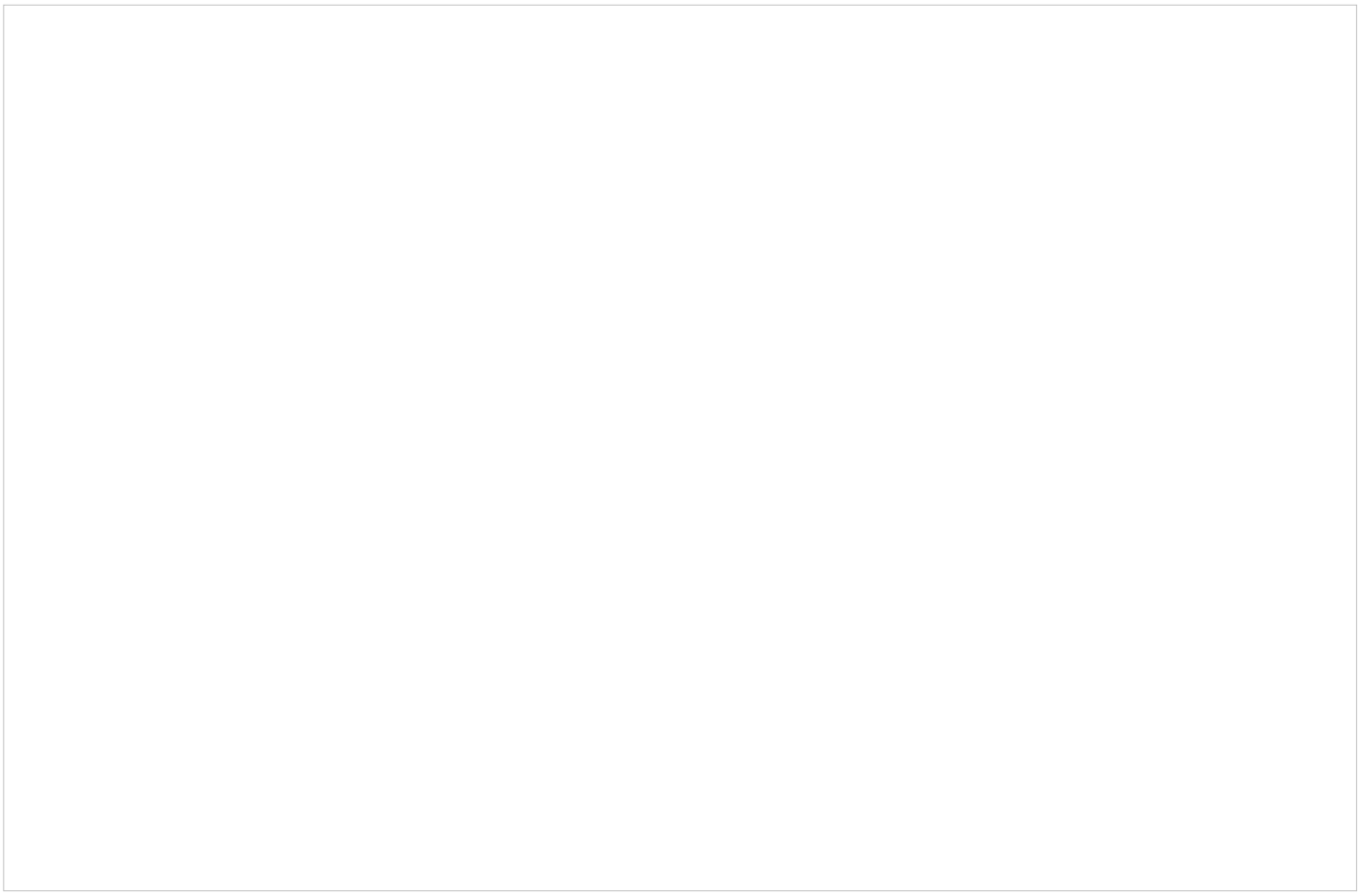
If after 4 weeks of treatment at the initial dose, the hemoglobin has not increased is by ≥1 g/dL (< 0,6 mmol/L), [and the reticulocyte count has not increased by ≥ 40,000 cells/µl above baseline], in the absence of red blood cell transfusion, the dose should be increased to 300 IU/kg 3 times per week or 60,000 IU weekly.

If after 4 weeks of additional therapy with 300 IU/kg three 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/µl] 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 increase < 40,000 cells/µl above baseline], response is unlikely and treatment should be discontinued.

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



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

Epoetin alfa therapy should be administered to patients with anaemia (e.g. Hb ≤ 11 g/dL{6.8 mmol/L).

SIDE EFFECTS

Clinical Trial Data

The most frequent adverse drug reaction during treatment with Epoetinum alfa is a dose-dependent increase in blood pressure or aggravation of existing hypertention. Monitoring of the blood pressure should be performed, particularly at the start of therapy. Other common adverse drug reactions observed in clinical trials of Epoetinum alfa are diarrhoea, nausea, headache, inflienza-like illness, pyrexia, rash, and vomiting. Influenza-like illness including headaches, joint pains, myalgia, and pyrexia may occur especially at the start of treatment.

Serious adverese drug reactions include venous and arterial thromboses and embolism (including some with fatal outcomes), such as deep venous thrombosis, pulmonary emboli, arterial thrombosis, retinal thrombosis, and shunt thrombosis (including dialysis equipment). In a cumulative analysis of 10 double-blind, randomized, placebo-controlled trials in subjects with cancer receiving chemotherapy, deep

venous thrombosis was reported in 2.1% and pulmonary embolism in 1.2% of the 1564 subjects exposed to Epoetinum alfa, compared to 1.2% and 1.2%, respectively, of the 1207 subjects exposed to placebo. Additionally, cerebrovascular accident (including cerebral infarction and cerebral haemorrhage) and transient ischaemic attacks have been reported in clinical trials of Epoetinum alfa.

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

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

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

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

System/Organ Class Adverse Drug Reaction	**EPREX Clinical Trial Data** Cancer	
	EPREX N=488 (%)	Placebo N=277(%)
Blood & Lymphatic System Disorders		
Thrombocytopenia	0.2	NR
Nerveous System Disorders		
Cerebral Haemorrhage*	0.41	NR
Seizure	0.2	NR
Headache	3.7	3.6
Vascular Disorders		
Deep Vein Thrombosis*	1.6	0.36
Hypertension	2.5	1.1
Gastrointestinal Disorders		
Nausea	17	32
Diarrhoea	5,7	4,4
vomiting	4.9	5,4
Skin and Subcutaneous Tissue Disorders		
Rash	1.2	1.1
Musculoskeletal, Connective Tissue, and Bone Disorders		
Arthalgia	1.4	1.8
Myalgia	1	1.4

General Disorders and Administration Site Conditions		
Influenza-like illness	4.9	3.3
Pyrexia	12	11
Injury, Poisoning, and Procedural Complications		
Shunt Thromboses (including dialysis equipment)	NA	NA

KEY: NR =not reported; NA = not applicable
*Including cases with a fatal outcome

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

Table 2. Additional Adverse Drug Reactions With Unknown Incidence Rate Identified in Other Clinical Trials of Epoetinum alfa

System/Organ Class Adverse Drug Reaction[b]
Immune System Disorders
Anaphylactic Reaction
Hypersensitivity
Nervous System Disorders
Cerebrovascular Accident[a]
Hypertensive Encephalopathy
Transient Ischaemic Attacks
Eye Disorders
Retinal Thrombosis
Vascular Disorders
Hypertensive Crisis
Arterial Thrombosis
Respiratory, Thoracic, and Mediastinal Disorders
Pulmonary embolism[a]
Skin and Subcutaneous Tissue Disorders
Urticaria
Angioneurotic oedema
Congenital and Familial/Genetic Disorders
Porphyria
General Disorders and Administration Site Conditions
Drug Ineffective
Peripheral Oedema
Injection Site Reaction

[a] Including cases with fatal outcomes

[b] Venous and arterial thromboembolic events have been reported in patients receiving EPREX (See Clinical Trial Data)

Cancer Patients
An increased incidence of thromboembolic events has been reported in cancer patients receiving ESAs, including Epoetinum alfa (see Special Warnings and Special Precaution for Use and Pharmacodynamic Properties)

Post-marketing data
Adverse drug reactions identified during the postmarketing experience with Epoetinum alfa also 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 report

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

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

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

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

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

In all patients receiving Epoetinum alfa, blood pressure should be closely monitored and controlled as necessary. Epoetinum alfa should be used with caution in the presence of untreated, inadequately treated or poorly controllable hypertension. Particular attention should be paid to the development of unusual headaches or an increase in headaches as a possible warning signal.

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

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

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

In all patients, haemoglobin level should be closely monitored due to a potential increased risk of thromboembolic events and fatal outcomes when patients are treated at haemoglobin levels above the target for the indication of use.

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

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

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

[The multidose preserved formulation contains benzyl alcohol. Benzyl alcohol has been reported to be associated with an increase incidence of neurological and other complications in premature infants which are sometimes fatal].

[Certain formulations of Epoetinum alfa contain albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk of transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral disease of CJD have been identified for albumin.]

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

Pure Red Cell Aplasia

Antibody-mediated pure red cell aplasia (PRCA) has been rarely reported after months to years of subcutaneous Epoetin treatment. In patients developing sudden lack of efficacy, defined by a decrease in haemoglobin (1 to 2 g/dL per month) with increased need for transfusions, a reticulocyte count should be obtained and typical causes of non-response (e.g., iron folate or Vitamin B_{12} deficiency, aluminium intoxication, infection or inflammation, blood loss haemolysis) should be investigated. If the reticulocyte count corrected for anaemia (i.e., the reticulocyte "index") is low (<20,000/mm^2 or <20,000/µl 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 ery-thropoietin, antibody-mediated PRCA is suspected, therapy with Epoetinum alfa should be discontinued immediately. No other erythropoietic therapy should be commenced because of the risk of cross-reaction. Appropriate therapy, such as blood transfusions, may be given to patients when indicated.

(Geriatric Use)

[Among 1051 patients enrolled in the 5 clinical studies of Epoetinum alfa for reduction of allogeneic blood transfusions in patients undergoing elective surgery 745 received Epoetinum alfa and 306 received placebo. Of the 745 patients who received Epoetinum alfa, 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 Epoetinum alfa 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 reqirements differ for this schedule.]

Cancer Patients

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

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

exceeded.

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

As an increased incidence of thrombotic vascular events (TVEs) has been observed in cancer patients receiving ESAs (see section Side Effects), this risk should be carefully weighed against the benefit to be derived from treatment with Epoetinum alfa particularly in cancer patients with increased risk factors of thrombotic vascular events, such as obesity and patients with a prior history of TVEs (e.g. deep venous thrombosis or pulmonary embolism). An investigational study (BEST study) in women with metastatic breast cancer was designed to determine whether Epoetinum alfa treatment that extended beyond the correction of anaemia could improve treatment outcomes. In that study the incidence of fatal thromboembolic events was higher inpatients receiving Epoetinum alfa than in those receiving placebo (see Pharmacodynamic Propeties).

In clinical studies ESAs shortened the time to tumour progression in patients with advanced head and neck cancer receiving radiation therapy when administered to target a haemoglobin of greater than 12g/dL. In the BEST study Epoetinum alfa shortened overall survival and increased deaths attributed to disease progression at 4 months in patients with metastatic breast cancer receiving chemotherapy when administered to target a haemoglobin of greater than 12 g/dL. See Pharmacodynamic properties.

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

A meta-analysis of 42 studies in patients with cancer treated with ESAs, within as well as beyond the recommended haemoglobin target, showed an overall survival hazard ratio of 1.08, (95% CI: 0.99, 1.18, 8167 patients) (see Pharmacodynamic Properties).

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

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

CONTRAINDICATIONS

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

Uncontrolled hypertension

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

All contraindicated associated with autologous blood predonation programmes should be respected in

patients being supplemented with Epoetinum alfa.

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

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

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

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

[The effect of Epoetinum alfa may be potentiated by the stimultaneous therapeutic administration of a haematinic agent, such as ferrous sulphate, when a defficiency state exists].

[Drugs that decrease erythropoeiesis may decrease the response to Epoetinum alfa.]

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

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

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

See Properties-Preclinical Safety Data-Reproduction Toxicology

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

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

Effect on ability to drive and use machines
None

Overdose
The therapeutic margin of Epoetinum alfa is very wide. Overdosage of Epoetinum alfa may produce effects that are extensions of the pharmacological effects of the hormone. Phlebotomy may be performed if excessively high haemoglobin levels occurs. Additional supportive care should be provided as necessary.

PHARMACEUTICALS PARTICULARS

List of excipients

- Polysorbate 80
- Sodium chloride
- Disodium phosphate dihydrate
- Sodium dihydrogen phosphate dihydrate
- Glycine
- Water for injections

Incompatibilities

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

Special precautions for storage

EPREX syringes and vials are to stored between 2˚C to 8˚C [36˚ F to 48° F] in the refrigerator, away from the freezer compartment. Do not freeze or shake. Keep the syringes and vials 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

Instructions for use and handling and disposal

[The product is for single use only]

The product should not be used, and should be discarded if:

- the seal is broken
- the liquid is coloured or
- particles are in it,
- it may have been frozen, or
- there has been a refrigeration failure

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

HOW SUPPLIED

EPREX 40000 IU/ml
Box@ 1 prefilled syringe @ 1 ml
Reg.No: DKI1060000843C1

HARUS DENGAN RESEP DOKTER

Manufactured by Vetter Pharma Ferligung GmbH, Germany
for Cilag GmbH International, Switzerland
Imported and distributed by PBF Johnson & Johnson Indonesia
A division of PT Johnson & Johnson Indonesia
Jakarta, Indonesia