1. NAME OF THE MEDICINAL PRODUCT

EPREX 2,000
EPREX 3,000
EPREX 4,000
EPREX 5,000
EPREX 6,000
EPREX 8,000
EPREX 10,000
EPREX 20,000
EPREX 30,000
EPREX 40,000

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

EPREX 4,000 IU/mL solution for injection in pre-filled syringe
Epoetin alfa 4,000 IU/mL (33.6 micrograms per mL), produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology

A pre-filled syringe of 0.5 mL contains 2,000 IU (16.8 micrograms) of epoetin alfa.

EPREX 10,000 IU/mL solution for injection in pre-filled syringe
Epoetin alfa 10,000 IU/mL (84.0 micrograms per mL), produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology

A pre-filled syringe of 0.3 mL contains 3,000 IU (25.2 micrograms) of epoetin alfa
A pre-filled syringe of 0.4 mL contains 4,000 IU (33.6 micrograms) of epoetin alfa
A pre-filled syringe of 0.5 mL contains 5,000 IU (42.0 micrograms) of epoetin alfa
A pre-filled syringe of 0.6 mL contains 6,000 IU (50.4 micrograms) of epoetin alfa
A pre-filled syringe of 0.8 mL contains 8,000 IU (67.2 micrograms) of epoetin alfa
A pre-filled syringe of 1.0 mL contains 10,000 IU (84.0 micrograms) of epoetin alfa

EPREX 40,000 IU/mL solution for injection in pre-filled syringe
Epoetin alfa 40,000 IU/mL (336.0 micrograms per mL), produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology

A pre-filled syringe of 0.5 mL contains 20,000 IU (168.0 micrograms) of epoetin alfa
A pre-filled syringe of 0.75 mL contains 30,000 IU (252.0 micrograms) of epoetin alfa
A pre-filled syringe of 1.0 mL contains 40,000 IU (336.0 micrograms) of epoetin alfa

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe.
Clear, colorless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of severe anemia associated with chronic renal failure, anemia in Zidovudine-treated HIV-infected patients, anemia in cancer patients on chemotherapy.

To increase the yield of autologous blood from patients in a predonation programme initiated to avoid the use of homologous blood.

Treatment is indicated in patients with moderate anemia (packed cell volume (PCV) approximately 33 to 39%, no iron deficiency) if blood conserving procedures are not available or insufficient either:
a: when the scheduled major elective surgery requires a large volume of blood (4 or more units of blood for females or 5 or more units for males)
or
b: when the period necessary to obtain the required volume of autologous blood is too short.

Perisurgery:
Reduction of allogeneic blood transfusion in surgery patients:
Eprex is indicated for the treatment of anemic patients (hemoglobin 9-11 g/dl) scheduled to undergo elective, noncardiac, nonvascular surgery to reduce the need for allogeneic blood transfusions.
Eprex is indicated for patients at high risk for peri-opertive transfusions with significant, anticipated blood loss.
Eprex is not indicated for anemic patients who are willing to donate autologous blood.
The safety of the perioperative use of Eprex has been studied only in patients who are receiving anticoagulant prophylaxis.
Eprex is indicated before surgeries known be associated with excessive blood loss (at least 2 units).

4.2 **Posology and method of administration**

Method of administration

As with any other injectable product, check that there are no particles in the solution or change in colour. Before use, leave the EPREX syringe to stand until it reaches room temperature. This usually takes between 15 and 30 minutes.

a) **Intravenous injection**: Administer over at least one to five minutes, depending on the total dose. In haemodialysed patients, a bolus injection may be given during the dialysis session through a suitable venous port in the dialysis line. Alternatively, the injection can be given at the end of the dialysis session via the fistula needle tubing, followed by 10 ml of isotonic saline to rinse the tubing and ensure satisfactory injection of the product into the circulation.

A slower injection is preferable in patients who react to the treatment with “flu-like” symptoms (see section 4.8).

Do not administer EPREX by intravenous infusion or in conjunction with other drug solutions.

subcutaneous injection: A maximum volume of 1 ml at one injection site should generally not be exceeded. In case of larger volumes, more than one site should be chosen for the injection.

The injections are given in the limbs or the anterior abdominal wall.
In those situations, in which 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.

Refer to section 3, How should the medicine be used? (instructions on how to inject EPREX) of the package leaflet.

Posology

All other causes of anaemia (iron, folate or Vitamin B_{12} 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 epoetin alfa, and when deciding to increase the dose. In order to ensure optimum response to epoetin alfa, adequate iron stores should be assured and iron supplementation should be administered if necessary (see section 4.4).

Treatment of symptomatic anaemia in adult and paediatric 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.

Treatment of symptomatic anaemia in adult chronic renal failure patients

Anaemia symptoms and sequelae may vary with age, gender, and co-morbid medical conditions; a physician's evaluation of the individual patient's clinical course and condition is necessary.

The recommended desired haemoglobin concentration range is between 10 g/dL to 12 g/dL (6.2 to 7.5 mmol/L). EPREX should be administered in order to increase haemoglobin to not greater than 12 g/dL (7.5 mmol/L). A rise in haemoglobin of greater than 2 g/dL (1.25 mmol/L) over a four week period should be avoided. If it occurs, appropriate dose adjustment should be made as provided.

Due to intra-patient variability, occasional individual haemoglobin values for a patient above and below the desired haemoglobin level may be observed. Haemoglobin variability should be addressed through dose management, with consideration for the haemoglobin target range of 10 g/dL (6.2 mmol/L) to 12 g/dL (7.5 mmol/L).

A sustained haemoglobin level of greater than 12 g/dL (7.5 mmol/L) should be avoided. If the haemoglobin is rising by more than 2 g/dL (1.25 mmol/L) per month, or if the sustained haemoglobin exceeds 12 g/dL (7.5 mmol/L) reduce the EPREX dose by 25%. If the haemoglobin exceeds 13 g/dL (8.1 mmol/L), discontinue therapy until it falls below 12 g/dL (7.5 mmol/L) and then reinstitute EPREX therapy at a dose 25% below the previous dose.

Patients should be monitored closely to ensure that the lowest approved effective dose of EPREX is used to provide adequate control of anaemia and of the symptoms of anaemia whilst maintaining a haemoglobin concentration below or at 12 g/dL (7.5 mmol/L).

Caution should be exercised with escalation of ESA doses in patients with chronic renal failure. In patients with a poor haemoglobin response to ESA, alternative explanations for the poor response should be considered (see section 4.4 and 5.1).

Adult haemodialysis patients

In patients on haemodialysis where intravenous access is readily available, administration by the intravenous route is preferable.

The treatment is divided into two stages:

Correction phase

50 IU/kg, 3 times per week.

If necessary, increase or decrease the dose by 25 IU/kg (3 times per week) until the desired haemoglobin concentration range between 10 g/dL to 12 g/dL (6.2 to 7.5 mmol/L) is achieved (this should be done in steps of at least four weeks).

Maintenance phase

The recommended total weekly dose is between 75 IU/kg and 300 IU/kg.
Appropriate adjustment of the dose should be made in order to maintain haemoglobin values within the desired concentration range between 10 g/dL to 12 g/dL (6.2 to 7.5 mmol/l).

The clinical data available suggest that those patients whose initial haemoglobin is very low (<6 g/dL or < 3.75 mmol/L) may require higher maintenance doses than those whose initial anaemia is less severe (> 8 g/dL or > 5 mmol/L).

Paediatric haemodialysis patients:

Anaemia symptoms and sequelae may vary with age, gender, and co-morbid medical conditions; a physician's evaluation of the individual patient's clinical course and condition is necessary.

In paediatric patients the recommended target haemoglobin range is between 9.5 and 11 g/dl (5.9-6.8 mmol/l).

EPREX should be administered in order to increase haemoglobin to not greater than 11 g/dl (6.8 mmol/l).

Patients should be monitored closely to ensure that the lowest approved dose of EPREX is used to provide adequate control of anaemia and of the symptoms of anaemia.

The treatment is divided into two stages:

In paediatric patients on haemodialysis where intravenous access is readily available, administration by the intravenous route is preferable.

Correction phase

The starting dose is 50 IU/kg intravenously, 3 times per week.

If necessary, increase or decrease the dose by 25 IU/kg (3 times per week) until the desired haemoglobin concentration range of between 9.5 g/dl to 11 g/dl (5.9 to 6.8 mmol/l) is achieved (this should be done in steps of at least four weeks).

Maintenance phase:

Appropriate adjustment of the dose should be made in order to maintain the haemoglobin levels within the desired range between 9.5 g/dl and 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.

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

Available data suggest that those patients whose initial haemoglobin is very low (<6.8 g/dl [4.25 mmol/l]) may require higher maintenance doses than those whose initial haemoglobin is higher (>6.8 g/dl [4.25 mmol/l]).

Adult 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

Starting dose of 50 IU/kg, 3 times per week, followed if necessary by a dosage increase with 25 IU/kg increments (3 times per week) until the desired goal is achieved (this should be done in steps of at least four weeks).

Maintenance phase

During the maintenance phase, EPREX can be administered either 3 times per week, and in the case of subcutaneous administration, once weekly or once every 2 weeks.

Appropriate adjustment of dose and dose intervals should be made in order to maintain haemoglobin 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, 240 IU/kg (up to a maximum of 20,000 IU) once weekly, or 480 IU/kg (up to a maximum of 40,000 IU) once every 2 weeks.

Adult peritoneal dialysis patients

Where intravenous access is not readily available EPREX may be administered subcutaneously. The treatment is divided into two stages:

Correction phase

Starting dose of 50 IU/kg, 2 times per week.

Maintenance phase

The recommended maintenance dose is between 25 IU/kg and 50 IU/kg, 2 times per week in 2 equal injections.

Appropriate adjustment of the dose should be made in order to maintain haemoglobin values at the desired level between 10 g/dL to 12 g/dL (6.2 to 7.5 mmol/L).

Treatment of patients with chemotherapy-induced anaemia

Anaemia symptoms and sequelae may vary with age, gender, and overall burden of disease; a physician's evaluation of the individual patient's clinical course and condition is necessary.

EPREX should be administered by the subcutaneous route to patients with anaemia (e.g. haemoglobin concentration ≤ 10 g/dL (6.2 mmol/L)).

Appropriate adjustment of the dose should be made in order to maintain haemoglobin concentrations within the desired concentration range between 10 g/dl and 12 g/dl (6.2 and 7.5 mmol/l).

Due to intra-patient variability, occasional individual haemoglobin concentrations for a patient above and below the desired haemoglobin concentration may be observed. Haemoglobin variability should be addressed through dose management, with consideration for the haemoglobin concentration range between 10 g/dL (6.2 mmol/l) and 12 g/dL (7.5 mmol/L). A sustained haemoglobin concentration of greater than 12 g/dl (7.5 mmol/L) should be avoided; guidance for appropriate dose adjustment for when haemoglobin values exceed 12 g/dL (7.5 mmol/L) are described below.

Epoetin alfa therapy should continue until one month after the end of chemotherapy. However, the need to continue Epoetin alfa therapy should be reevaluated periodically.

The initial dose is 150 IU/kg given subcutaneously 3 times per week.

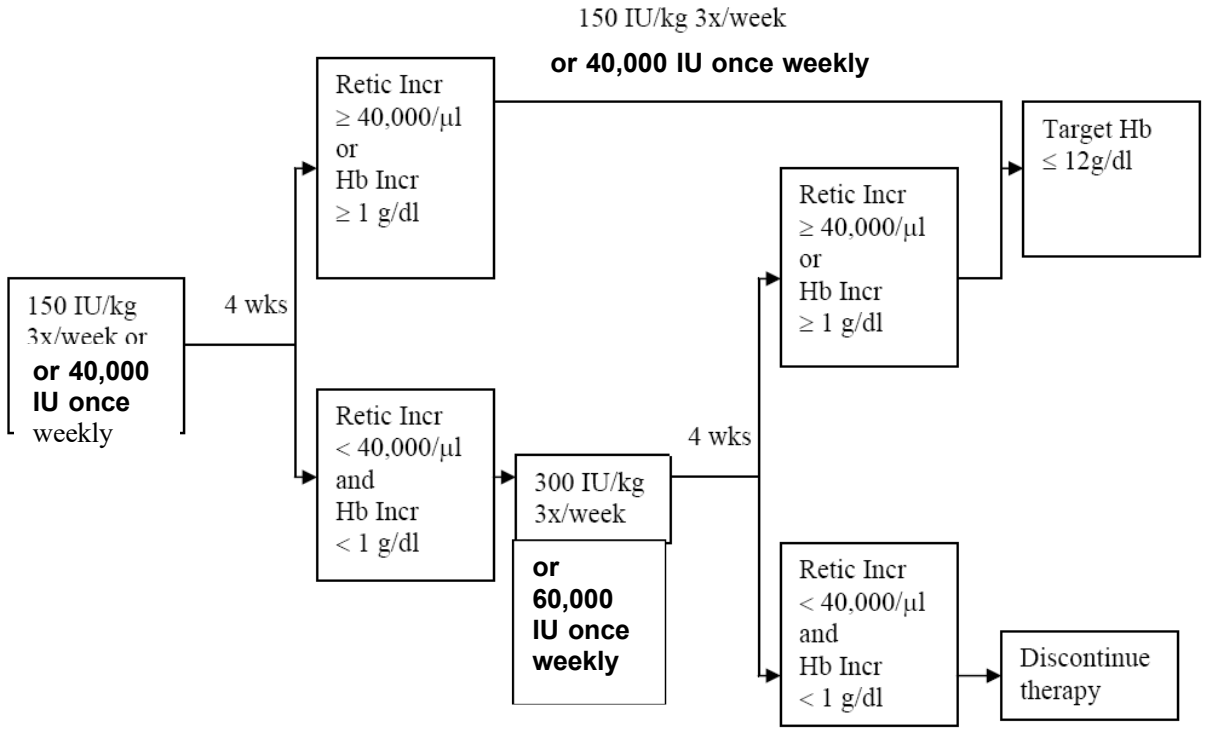
Alternatively, EPREX can be administered at an initial dose of 40,000IU once weekly.

If the haemoglobin has increased by at least 1 g/dL (0.62 mmol/L) or the reticulocyte count has increased ≥ 40,000 cells/mL above baseline after 4 weeks of treatment, the dose should remain at 150 IU/kg 3 times per week or 40,000IU once weekly.

If the haemoglobin increase is < 1 g/dL (< 0.62 mmol/L) and the reticulocyte count has increased < 40,000 cells/mL above baseline, increase the dose to 300 IU/kg 3 times per week *or 60,000 IU once weekly.*

. If after an additional 4 weeks of therapy at 300 IU/kg 3 times per week or 60,000 IU once weekly, the haemoglobin has increased ≥ 1 g/dL (≥ 0.62 mmol/L) or the reticulocyte count has increased ≥ 40,000 cells/mL, the dose should remain at 300 IU/kg 3 times per week or 60,000 IU once weekly.

However, if the haemoglobin has increased < 1 g/dL (< 0.62 mmol/L) and the reticulocyte count has increased < 40,000 cells/mL above baseline, response is unlikely and treatment should be discontinued.
The recommended dosing regimen is described in the following diagram:



Patients should be monitored closely to ensure that the lowest approved dose of erythropoiesis-stimulating agent (ESA) is used to provide adequate control of the symptoms of anaemia.

Dose adjustment to maintain haemoglobin concentrations between 10g/dl 12 g/dl:

If the haemoglobin is rising by more than 2 g/dl (1.25 mmol/l) per month, or if the haemoglobin exceeds 12 g/dl (7.5 mmol/l), reduce the epoetin alfa dose by about 25 50%.

If the haemoglobin exceeds 12g/dL (7.5mmol/l), discontinue therapy until it falls below 12 g/dl (7.5 mmol/l) and then reinstitute epoetin alfa therapy at a dose 25% below the previous dose.

<u>Adult</u> surgery patients in an autologous predonation programme

The intravenous route of administration should be used. At the time of donating blood, epoetin alfa should be administered after the completion of the blood donation procedure.

Mildly anaemic patients (haematocrit of 3339%) requiring predeposit of ≥ 4 units of blood should be treated with epoetin alfa at 600 IU/kg, 2 times weekly for 3 weeks prior to surgery.

<u>Adult</u> patients scheduled for major elective orthopaedic surgery

The subcutaneous route of administration should be used.

Prior to initiating treatment with EPREX a hemoglobin level should be obtained to establish that it is 10g/dL ± 1.

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

In cases where there is a medical need to shorten the lead time before surgery to less than three weeks, 300 IU/kg epoetin alfa should be given daily for 10 consecutive days prior to surgery, on the day of surgery and for four days immediately thereafter.

When performing haematologic assessments during the preoperative period, if the haemoglobin level reaches 15 g/dl, or higher, administration of epoetin alfa should be stopped and further dosages should not be given.

Care should be taken to ensure that at the outset of the treatment patients are not iron-deficient.

Zidovudine-treated HIV-infected patients

Prior to beginning EPREX, it is recommended that the endogenous serum erythropoietin level be determined (prior to transfusion). Available evidence suggests that patients receiving zidovudine with endogenous serum erythropoietin levels > 500 mUnits/mL are unlikely to respond to therapy with EPREX**.**

Responsiveness to EPREX in HIV-infected patients is dependent upon the endogenous serum erythropoietin level prior to treatment. Patients with endogenous serum erythropoietin levels ≤ 500 mUnits/mL, and who are receiving a dose of zidovudine ≤ 4,200 mg/week, may respond to EPREX therapy.

Patients with endogenous serum erythropoietin levels > 500 mUnits/mL do not appear to respond to EPREX therapy. In a series of four clinical trials involving 255 patients, 60% to 80% of HIV-infected patients treated with zidovudine had endogenous serum erythropoietin levels ≤ 500 mUnits/mL. Response to EPREX in zidovudine-treated HIV-infected patients is manifested by reduced transfusion requirements and increased hematocrit.

In zidovudine-treated HIV-infected patients the dosage of Eprex should be titrated for each patient to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for blood transfusion and not to exceed the upper safety limit of 12 g/dL.

Starting Dose*: For* ***adult patients with*** serum erythropoietin levels ≤500 mUnits/mL who are receiving a dose of zidovudine ≤4200 mg/week, the recommended starting dose of EPREX is 100 IU/kg as an I.V. or S.C. injection TIW (three times a week) for 8 weeks.

Increase Dose: During the dose adjustment phase of therapy, the hemoglobin should be monitored weekly. If the response is not satisfactory in terms of reducing transfusion requirements or increasing hemoglobin after 8 weeks of therapy, the dose of EPREX can be increased by 50 to 100 Units/kg TIW. Response should be evaluated every 4 to 8 weeks thereafter and the dose adjusted accordingly by 50 to 100 Units/kg increments TIW. If patients have not responded satisfactorily to an EPREX dose of 300 Units/kg TIW, it is unlikely that they will respond to higher doses of EPREX. Discontinue EPREX if an increase in hemoglobin is not achieved at a dose of 300 Units/kg for 8 weeks.

Maintenance Dose: After attainment of the desired response (ie, reduced transfusion requirements or increased hemoglobin), the dose of EPREX should be titrated to maintain the response based on factors such as variations in zidovudine dose and the presence of intercurrent infectious or inflammatory episodes. If the haemoglobin exceeds **the upper safety limit of 12** g/dL, the dose should be discontinued until the hemoglobin drops to **11** g/dL. The dose should be reduced by 25% when treatment is resumed and then titrated to maintain the desired hemoglobin.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Patients who develop pure red cell aplasia (PRCA) following treatment with any erythropoietin should not receive EPREX or any other erythropoietin (see section 4.4 - *Pure Red Cell Aplasia*).

Uncontrolled hypertension.

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.

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

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General

In all patients receiving epoetin alfa, blood pressure should be closely monitored and controlled as necessary. Epoetin alfa should be used with caution in the presence of untreated, inadequately treated or poorly controllable hypertension. It may be necessary to add or increase anti-hypertensive treatment. If blood pressure cannot be controlled, epoetin alfa 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 epoetin alfa treatment in patients with previously normal or low blood pressure. Particular attention should be paid to sudden stabbing migraine-like headaches as a possible warning signal (see section 4.8).

Epoetin alfa 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.

Epoetin alfa should be used with caution in patients with chronic liver failure. The safety of epoetin alfa has not been established in patients with hepatic dysfunction.

An increased incidence of thrombotic vascular events (TVEs) has been observed in patients receiving ESAs (see section 4.8). 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 these TVEs should be carefully weighed against the benefits to be derived from treatment with epoetin alfa particularly in patients with pre-existing risk factors for TVE, including obesity and prior history of TVEs (e.g., deep venous thrombosis, pulmonary embolism, and cerebral vascular accident).

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

There may be a moderate dose-dependent rise in the platelet count within the normal range during treatment with epoetin 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 is regularly monitored during the first 8 weeks of therapy.

All other causes of anaemia (iron, folate or Vitamin B_{12} 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 epoetin alfa, 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 epoetin alfa, adequate iron stores should be assured and iron supplementation should be administered if necessary (see section 4.2) For the selection of the best treatment option according to the patient's needs, current treatment guidelines on iron supplementation in combination with dose instructions approved and outlined in the Prescribing Information of the iron medication should be followed:

- For chronic renal failure patients, iron supplementation is recommended if serum ferritin levels are below 100 ng/mL.

- For cancer patients, iron supplementation is recommended if transferrin saturation is below 20%.

- For patients in an autologous predonation programme, iron supplementation should be administered several weeks prior to initiating the autologous predeposit in order to achieve high iron stores prior to starting epoetin alfa therapy, and throughout the course of epoetin alfa therapy.

- For patients scheduled for major elective orthopaedic surgery, iron supplementation should be administered throughout the course of epoetin alfa therapy. If possible, iron supplementation should be initiated prior to starting epoetin alfa therapy to achieve adequate iron stores.

Very rarely, development of or exacerbation of porphyria has been observed in epoetin alfa-treated patients. Epoetin alfa should be used with caution in patients with porphyria.

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported in association with epoetin treatment. More severe cases have been observed with long-acting epoetins.

At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, EPREX should be withdrawn immediately and an alternative treatment considered.

If the patient has developed a severe cutaneous skin reaction such as SJS or TEN due to the use of EPREX treatment with EPREX must not be restarted in this patient at any time.

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

Patients should only be switched from one ESA to another under appropriate supervision.

Pure Red Cell Aplasia

Antibody-mediated pure red cell aplasia (PRCA) has been reported after months to years of epoetin alfa treatment.

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

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 and bone marrow fibrosis of any origin) should be investigated.

A paradoxical decrease in haemoglobin and development of severe anaemia associated with low reticulocyte counts should prompt to discontinue treatment with epoetin alfa and perform anti-erythropoietin antibody testing. A bone marrow examination should also be considered for diagnosis of PRCA.

No other ESA therapy should be commenced because of the risk of cross-reaction.
Treatment of symptomatic anaemia in adult and paediatric chronic renal failure patients
Chronic renal failure patients being treated with epoetin alfa should have haemoglobin levels measured on a regular basis until a stable level is achieved, and periodically thereafter.

In chronic renal failure patients the rate of increase in haemoglobin should be approximately 1 g/dL (0.62 mmol/L) per month and should not exceed 2 g/dL (1.25 mmol/L) per month to minimise risks of an increase in hypertension.

In patients with chronic renal failure, maintenance haemoglobin concentration should not exceed the upper limit of the haemoglobin concentration range as recommended in section 4.2. In clinical trials, an increased risk of death and serious cardiovascular events was observed when ESAs were administered to achieve a haemoglobin concentration level of greater than 12 g/dL (7.5 mmol/L).

Controlled clinical trials have not shown significant benefits attributable to the administration of epoetins when haemoglobin concentration is increased beyond the level necessary to control symptoms of anaemia and to avoid blood transfusion.

Caution should be exercised with escalation of EPREX doses in patients with chronic renal failure since high cumulative epoetin doses may be associated with an increased risk of mortality, serious cardiovascular and cerebrovascular events. In patients with a poor haemoglobin response to epoetins, alternative explanations for the poor response should be considered (see section 4.2 and 5.1).

Chronic renal failure patients treated with epoetin alfa by the subcutaneous route should be monitored regularly for loss of efficacy, defined as absent or decreased response to epoetin alfa treatment in patients who previously responded to such therapy. This is characterised by a sustained decrease in haemoglobin despite an increase in epoetin alfa dosage (see section 4.8).

Some patients with more extended dosing intervals (greater than once weekly) of epoetin alfa may not maintain adequate haemoglobin levels (see section 5.1) and may require an increase in epoetin alfa dose. Haemoglobin levels should be monitored regularly.

Shunt thromboses have occurred in haemodialysis patients, especially in those who have a tendency to hypotension or whose arteriovenous fistulae exhibit complications (e.g. stenoses, aneurysms, etc.). Early shunt revision and thrombosis prophylaxis by administration of acetylsalicylic acid, for example, is recommended in these patients.
Hyperkalaemia has been observed in isolated cases though 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 appropriate treatment of the hyperkalaemia, consideration should be given to ceasing epoetin alfa administration until the serum potassium level has been corrected.

An increase in heparin dose during haemodialysis is frequently required during the course of therapy with epoetin alfa as a result of the increased packed cell volume. Occlusion of the dialysis system is possible if heparinisation is not optimum.

Based on information available to date, correction of anaemia with epoetin alfa in adult patients with renal insufficiency not yet undergoing dialysis does not accelerate the rate of progression of renal insufficiency.

Treatment of patients with chemotherapy-induced anaemia

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

Epoetins 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 epoetins could stimulate the growth of tumours.

The role of ESAs on tumour progression or reduced progression-free survival cannot be excluded. In controlled clinical studies, use of epoetin alfa and other ESAs have been associated with decreased locoregional tumour control or decreased overall survival:

- decreased locoregional control in patients with advanced head and neck cancer receiving radiation therapy when administered to achieve a haemoglobin 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 achieve a haemoglobin concentration range of 12 to 14 g/dL (7.5 to 8.7 mmol/L),
- increased risk of death when administered to achieve a haemoglobin 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,
- an observed 9% increase in risk for PD or death in the epoetin alfa plus SOC group from a primary analysis and a 15% increased risk that cannot be statistically ruled out in patients with metastatic breast cancer receiving chemotherapy when administered to achieve a haemoglobin concentration range of 10 to 12 g/dL (6.2 to 7.5 mmol/L).

In view of the above, in some clinical situations blood transfusion should be the preferred treatment for the management of anaemia in patients with cancer. 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 that should be considered in this assessment should 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 section 5.1).

In cancer patients receiving chemotherapy, the 2 to 3 week delay between ESA administration and the appearance of erythropoietin-induced red cells should be taken into account when assessing if epoetin alfa therapy is appropriate (patient at risk of being transfused).

Surgery patients in autologous predonation programmes

All special warnings and special precautions associated with autologous predonation programmes, especially routine volume replacement, should be respected.

Patients scheduled for major elective orthopaedic surgery

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, the possibility that epoetin alfa treatment may be associated with an increased risk of

postoperative thrombotic/vascular events cannot be excluded. Therefore, epoetin alfa should not be used in patients with baseline haemoglobin > 13 g/dL.

Excipients

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium free."

Polysorbate 80

This medicine contains a maximum of 0.30 mg of polysorbate 80 (E 433) in each syringe, equivalent to a concentration of 0.30 mg/mL. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No evidence exists that indicates that treatment with epoetin alfa alters the metabolism of other drugs. Drugs that decrease erythropoiesis may decrease the response to epoetin alfa.

Since cyclosporin is bound by RBCs there is potential for a drug interaction. If epoetin 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 epoetin alfa and G-CSF or GM-CSF with regard to haematological differentiation or proliferation of tumour biopsy specimens *in vitro*.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Studies in animals have shown reproduction toxicity (see section 5.3). Consequently, epoetin alfa should be used in pregnancy only if the potential benefit outweighs the potential risk to the foetus. The use of epoetin alfa is not recommended in pregnant surgical patients participating in an autologous blood predonation.

Breastfeeding

It is not known whether exogenous epoetin alfa is excreted in human milk. Epoetin alfa should be used with caution in nursing women. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with epoetin alfa should be made taking into account the benefit of breast-feeding to the child and the benefit of epoetin alfa therapy to the woman.

The use of epoetin alfa is not recommended in lactating surgical patients participating in an autologous blood predonation programme.

Fertility

There are no studies assessing the potential effect of epoetin alfa on male or female fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of Safety Profile

The most frequent adverse drug reaction during treatment with epoetin alfa is a dose-dependent increase in blood pressure or aggravation of existing hypertension. Monitoring of the blood pressure should be performed, particularly at the start of therapy (see section 4.4).

The most frequently occurring adverse drug reactions observed in clinical trials of epoetin alfa are diarrhoea, 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 section 4.4).

Tabulated List of Adverse Reactions

Of a total 3,417 subjects in 25 randomised, double-blinded, placebo or standard of care controlled studies, the overall safety profile of EPREX was evaluated in 2,094 anaemic subjects. Included were 228 epoetin alfa-treated CRF subjects in 4 chronic renal failure studies (2 studies in predialysis [N = 131 exposed CRF subjects] and 2 in dialysis [N = 97 exposed CRF subjects]; 1,404 exposed cancer subjects in 16 studies of anaemia due to chemotherapy; 147 exposed subjects in 2 studies for autologous blood donation; 213 exposed subjects in 1 study in the perisurgical period. Adverse drug reactions reported by ≥1% of subjects treated with epoetin alfa in these trials are shown in the table below.

Frequency estimate: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very Rare (< 1/10,000), Not known (cannot be estimated from the available data).

MedDRA System Organ Classification (SOC)	**Adverse Reaction (Preferred Term Level)**	**Frequency**
Blood and lymphatic system disorders	Pure red cell aplasia[3], Thrombocythaemia	Rare
Metabolism and nutrition disorders	Hyperkalaemia[1]	Uncommon
Immune system disorders	Hypersensitivity[3]	Uncommon
	Anaphylactic reaction[3]	Rare
Nervous system disorders	Headache	Common
	Convulsion	Uncommon
Vascular disorders	Hypertension, Venous and arterial thromboses[2]	Common
	Hypertensive crisis[3]	Not known
Respiratory, thoracic and mediastinal disorders	Cough	Common
	Respiratory tract congestion	Uncommon
Gastrointestinal disorders	Diarrhoea, Nausea, Vomiting	Very common
Skin and subcutaneous tissue disorders	Rash	Common
	Urticaria[3]	Uncommon
	Angioneurotic oedema[3]	Not known
Musculoskeletal and connective tissue disorders	Arthralgia, Bone pain, Myalgia, Pain in extremity	Common
Congenital, familial and genetic disorders	Porphyria acute[3]	Rare

General disorders and administration site conditions	Pyrexia	Very common
	Chills, Influenza like illness, Injection site reaction, Oedema peripheral	Common
	Drug ineffective[3]	Not known
Investigations	Anti-erythropoeitin antibody positive	Rare

[1] Common in dialysis

[2] 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 (including cerebral infarction and cerebral haemorrhage) transient ischaemic attacks, and shunt thrombosis (including dialysis equipment) and thrombosis within arteriovenous shunt aneurisms

[3] Addressed in the subsection below and/or in section 4.4

Description of selected adverse reactions

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

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported in association with epoetin treatment (see section 4.4).

Hypertensive crisis with encephalopathy and seizures, requiring the immediate attention of a physician and intensive medical care, have occurred also during epoetin alfa treatment in patients with previously normal or low blood pressure. Particular attention should be paid to sudden stabbing migraine-like headaches as a possible warning signal (see section 4.4).

Antibody-mediated pure red cell aplasia has been very rarely reported in < 1/10,000 cases per patient year after months to years of treatment with EPREX (see section 4.4). More cases have been reported with subcutaneous (SC) route of administration, compared with the IV route.

Paediatric population with chronic renal failure on haemodialysis

The exposure of paediatric patients with chronic renal failure on haemodialysis in clinical trials and post-marketing experience is limited. No paediatric-specific adverse reactions not mentioned previously in the table above, or any that were not consistent with the underlying disease were reported in this population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form *http://sideeffects.health.gov.il*

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-anaemic, 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 (epoetin 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.

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

Pharmacodynamic effects

Healthy volunteers

After single doses (20,000 to 160,000 IU subcutaneously) of epoetin alfa, a dose-dependent response was observed for the pharmacodynamic markers investigated including: reticulocytes, RBCs, and haemoglobin. A defined concentration-time profile with peak and return to baseline was observed for changes in percent reticulocytes. A less defined profile was observed for RBCs and haemoglobin. In general, all pharmacodynamic markers increased in a linear manner with dose reaching a maximum response at the highest dose levels.

Further pharmacodynamic studies explored 40,000 IU once weekly versus 150 IU/kg 3 times per week. Despite differences in concentration-time profiles the pharmacodynamic response (as measured by changes in percent reticulocytes, haemoglobin, and total RBCs) was similar between these regimens. Additional studies compared the 40,000 IU once-weekly regimen of epoetin alfa with biweekly doses ranging from 80,000 to 120,000 IU subcutaneously. Overall, based on the results of these pharmacodynamic studies in healthy subjects, the 40,000 IU once-weekly dosing regimen seems to be more efficient in producing RBCs than the biweekly regimens despite an observed similarity in reticulocyte production in the once-weekly and biweekly regimens.

Chronic renal failure

Epoetin alfa has been shown to stimulate erythropoiesis in anaemic patients with CRF, including dialysis and pre-dialysis patients. The first evidence of a response to epoetin alfa is an increase in the reticulocyte count within 10 days, followed by increases in the red cell count, haemoglobin and haematocrit, usually within 2 to 6 weeks. The haemoglobin response varies between patients and may be impacted by iron stores and the presence of concurrent medical problems.

Chemotherapy-induced anaemia
Epoetin alfa administered 3 times per week or once weekly has been shown to increase haemoglobin and decrease transfusion requirements after the first month of therapy in anaemic cancer patients receiving chemotherapy.

In a study comparing the 150 IU/kg, 3 times-per-week and 40,000 IU, once-weekly dosing regimens in healthy subjects and in anaemic cancer subjects the time profiles of changes in percent reticulocytes, haemoglobin, and total red blood cells were similar between the two dosing regimens in both healthy and anaemic cancer subjects. The AUCs of the respective pharmacodynamic parameters were similar between the 150 IU/kg, 3 times-per-week and 40,000 IU, once-weekly dosing regimens in healthy subjects and also in anaemic cancer subjects.

Adult surgery patients in an autologous predonation programme
Epoetin alfa has been shown to stimulate red blood cell production in order to augment autologous blood collection, and to limit the decline in haemoglobin in adult patients scheduled for major elective surgery who are not expected to predeposit their complete perioperative blood needs. The greatest effects are observed in patients with low haemoglobin (≤ 13 g/dL).

Treatment of adult patients scheduled for major elective orthopaedic surgery
In patients scheduled for major elective orthopaedic surgery with a pretreatment haemoglobin of > 10 to ≤ 13 g/dL, epoetin alfa has been shown to decrease the risk of receiving allogeneic transfusions and hasten erythroid recovery (increased haemoglobin levels, haematocrit levels, and reticulocyte counts).

Clinical efficacy and safety

Chronic renal failure
Epoetin alfa has been studied in clinical trials in adult anaemic CRF patients, including haemodialysis and pre-dialysis patients, to treat anaemia and maintain haematocrit within a target concentration range of 30 to 36%.

In clinical trials at starting doses of 50 to 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 target haematocrit 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 to 36% was approximately 75 IU/kg given 3 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 that 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 to 150 IU/kg per week have been shown to maintain haematocrits of 36 to 38% for up to six months.

In 2 studies with extended interval dosing of EPREX (3 times per week, once weekly, once every 2 weeks, and once every 4 weeks) some patients with longer dosing intervals did not maintain adequate haemoglobin levels and reached protocol-defined haemoglobin withdrawal criteria (0% in once weekly, 3.7% in once-every-2-weeks, and 3.3% in the once-every-4-weeks groups).

A randomised prospective trial (CHOIR) evaluated 1,432 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 haemoglobin concentration level) or
11.3 g/dL. A major cardiovascular event (death, myocardial infarction, stroke or hospitalisation 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).

Pooled post-hoc analyses of clinical studies of ESAs have been performed in chronic renal failure patients (on dialysis, not on dialysis, in diabetic and non-diabetic patients). A tendency towards increased risk estimates for all-cause mortality, cardiovascular and cerebrovascular events associated with higher cumulative ESA doses independent of the diabetes or dialysis status was observed (see section 4.2 and section 4.4).

Treatment of patients with chemotherapy-induced anaemia

Epoetin alfa has been studied in clinical trials in adult anaemic cancer patients with lymphoid and solid tumours, and patients on various chemotherapy regimens, including platinum and non-platinum- containing regimens. In these trials, epoetin alfa administered 3 times per week 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 patients with haematological malignancies and solid tumours respond equivalently to epoetin alfa therapy, and that patients with or without tumour infiltration of the bone marrow respond equivalently to epoetin alfa therapy. 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 1,000 and 500 cells/µL.

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). Two other smaller, randomised, placebo-controlled trials failed to show a significant improvement in quality of life parameters on the EORTC-QLQ-C30 scale or CLAS, respectively.

Survival and tumour progression have been examined in five large controlled studies involving a total of 2,833 patients, of which four were double-blind placebo-controlled studies and one was an open- label study. The studies either recruited patients who were being treated with

chemotherapy (two studies) or used patient populations in which ESAs are not indicated: anaemia in patients with cancer not receiving chemotherapy, and head and neck cancer patients receiving radiotherapy. The desired haemoglobin concentration level in two studies was > 13 g/dL; in the remaining three studies it was 12 to 14 g/dL. In the open-label study there was no difference in overall survival between patients treated with recombinant human erythropoietin and controls. In the four placebo-controlled studies the hazard ratios for overall survival ranged between 1.25 and 2.47 in favour of controls. These studies have shown a consistent unexplained statistically significant excess mortality in patients who have anaemia associated with various common cancers who received recombinant human erythropoietin compared to controls. Overall survival outcome in the trials could not be satisfactorily explained by differences in the incidence of thrombosis and related complications between those given recombinant human erythropoietin and those in the control group.

A patient-level data analysis has also been performed on more than 13,900 cancer patients (chemo-, radio-, chemoradio-, or no therapy) participating in 53 controlled clinical trials involving several epoetins. Meta-analysis of overall survival data produced a hazard ratio point estimate of 1.06 in favour of controls (95% CI: 1.00, 1.12; 53 trials and 13,933 patients) and for the cancer patients receiving chemotherapy, the overall survival hazard ratio was 1.04 (95% CI: 0.97, 1.11; 38 trials and 10,441 patients). Meta-analyses also indicate consistently a significantly increased relative risk of thromboembolic events in cancer patients receiving recombinant human erythropoietin (see section 4.4).

A randomised, open-label, multicentre study was conducted in 2,098 anaemic women with metastatic breast cancer, who received first line or second line chemotherapy. This was a non-inferiority study designed to rule out a 15% risk increase in tumour progression or death of epoetin alfa plus standard of care (SOC) as compared with SOC alone. At the time of clinical data cutoff, 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. 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).

Autologous predonation programme

The effect of epoetin alfa in facilitating autologous blood donation in patients with low haematocrits (≤ 39% and no underlying anaemia due to iron deficiency) scheduled for major orthopaedic surgery was evaluated in a double-blind, placebo-controlled study conducted in 204 patients, and a single-blind placebo controlled study in 55 patients.

In the double-blind study, patients were treated with epoetin alfa 600 IU/kg or placebo intravenously once daily every 3 to 4 days over 3 weeks (total 6 doses). On average, patients treated with epoetin alfa were able to predeposit significantly more units of blood (4.5 units) than placebo-treated patients (3.0 units).

In the single-blind study, patients were treated with epoetin alfa 300 IU/kg or 600 IU/kg or placebo intravenously once daily every 3 to 4 days over 3 weeks (total 6 doses). Patients treated with epoetin alfa were also able to predeposit significantly more units of blood (epoetin alfa 300 IU/kg = 4.4 units; epoetin alfa 600 IU/kg = 4.7 units) than placebo-treated patients (2.9 units).

Epoetin alfa therapy reduced the risk of exposure to allogeneic blood by 50% compared to patients not receiving epoetin alfa.

Major elective orthopaedic surgery

The effect of epoetin alfa (300 IU/kg or 100 IU/kg) on the exposure to allogeneic blood transfusion has been evaluated in a placebo-controlled, double-blind clinical trial in non-iron deficient adult patients scheduled for major elective orthopaedic hip or knee surgery. Epoetin alfa was administered subcutaneously for 10 days prior to surgery, on the day of surgery, and for four days after surgery.

Patients were stratified according to their baseline haemoglobin (≤ 10 g/dL, > 10 to ≤ 13 g/dL and > 13 g/dL).

Epoetin alfa 300 IU/kg significantly reduced the risk of allogeneic transfusion in patients with a pretreatment haemoglobin of > 10 to ≤ 13 g/dL. Sixteen percent of epoetin alfa 300 IU/kg, 23% of epoetin alfa 100 IU/kg and 45% of placebo-treated patients required transfusion.

An open-label, parallel-group trial in non-iron deficient adult subjects with a pretreatment haemoglobin of ≥ 10 to ≤ 13 g/dL who were scheduled for major orthopaedic hip or knee surgery compared epoetin alfa 300 IU/kg subcutaneously daily for 10 days prior to surgery, on the day of surgery and for four days after surgery to epoetin alfa 600 IU/kg subcutaneously once weekly for 3 weeks prior to surgery and on the day of surgery.

From pretreatment to presurgery, the mean increase in haemoglobin in the 600 IU/kg weekly group (1.44 g/dL) was twice than that observed in the 300 IU/kg daily group (0.73 g/dL). Mean haemoglobin levels were similar for the two treatment groups throughout the postsurgical period.

The erythropoietic response observed in both treatment groups resulted in similar transfusion rates (16% in the 600 IU/kg weekly group and 20% in the 300 IU/kg daily group).

Paediatric population

Chronic Renal Failure

Epoetin alfa was evaluated in an open-label, non-randomised, open dose-range, 52-week clinical study in paediatric CRF patients undergoing haemodialysis. The median age of patients enrolled in the study was 11.6 years (range 0.5 to 20.1 years).

Epoetin alfa was administered at 75 IU/kg/week intravenously in 2 or 3 divided doses post-dialysis, titrated by 75 IU/kg/week at intervals of 4 weeks (up to a maximum of 300 IU/kg/week), to achieve a 1 g/dL/month increase in haemoglobin. The desired haemoglobin concentration range was 9.6 to
11.2 g/dL. Eighty-one percent of patients achieved the haemoglobin concentration level. The median time to target was 11 weeks and the median dose at target was 150 IU/kg/week. Of the patients who achieved the target, 90% did so on a 3 times-per-week dosing regimen.

After 52 weeks, 57% of patients remained in the study, receiving a median dose of 200 IU/kg/week.

Clinical data with subcutaneous administration in children are limited. In 5 small, open label, uncontrolled studies (number of patients ranged from 9-22, total N=72), Epoetin alfa has been administered subcutaneously in children at starting doses of 100 IU/kg/week to 150 IU/kg/week with the possibility to increase up to 300 IU/kg/week. In these studies, most were predialysis patients (N=44), 27 patients were on peritoneal dialysis and 2 were on haemodialysis with age

ranging from 4 months to 17 years. Overall, these studies have methodological limitations but treatment was associated with positive trends towards higher haemoglobin levels. No unexpected adverse events were reported (see section 4.2).

Chemotherapy-induced anaemia

Epoetin alfa 600 IU/kg (administered intravenously or subcutaneously once weekly) has been evaluated in a randomised, double-blind, placebo-controlled, 16-week study and in a randomised, controlled, open-label, 20-week study in anaemic paediatric patients receiving myelosuppressive chemotherapy for the treatment of various childhood non-myeloid malignancies.

In the 16-week study (n=222), in the epoetin alfa-treated patients there was no statistically significant effect on patient-reported or parent-reported Paediatric Quality of Life Inventory or Cancer Module scores compared with placebo (primary efficacy endpoint). In addition, there was no statistical difference between the proportion of patients requiring pRBC transfusions between the Epoetin alfa group and placebo.

In the 20-week study (n=225), no significant difference was observed in the primary efficacy endpoint,
i.e. the proportion of patients who required a RBC transfusion after Day 28 (62% of epoetin alfa patients versus 69% of standard therapy patients).

5.2 Pharmacokinetic properties

Absorption

Following subcutaneous injection, serum levels of epoetin alfa reach a peak between 12 and 18 hours post-dose. There was no accumulation after multiple dose administration of 600 IU/kg administered subcutaneously weekly.

The absolute bioavailability of subcutaneous injectable epoetin alfa is approximately 20% in healthy subjects.

Distribution

The mean volume of distribution was 49.3 mL/kg after intravenous doses of 50 and 100 IU/kg in healthy subjects. Following intravenous administration of epoetin alfa in subjects with chronic renal failure, the volume of distribution ranged from 57-107 mL/kg after single dosing (12 IU/kg) to 42- 64 mL/kg after multiple dosing (48-192 IU/kg), respectively. Thus, the volume of distribution is slightly greater than the plasma space.

Elimination

The half-life of epoetin alfa following multiple dose intravenous administration is approximately 4 hours in healthy subjects. The half-life for the subcutaneous route is estimated to be approximately 24 hours in healthy subjects.

The mean CL/F for the 150 IU/kg 3 times-per-week and 40,000 IU once-weekly regimens in healthy subjects were 31.2 and 12.6 mL/h/kg, respectively. The mean CL/F for the 150 IU/kg, 3-times-per- week and 40,000 IU, once-weekly regimens in the anaemic cancer subjects were 45.8 and
11.3 mL/h/kg, respectively. In most anaemic subjects with cancer receiving cyclic chemotherapy CL/F was lower after subcutaneous doses of 40,000 IU once weekly and 150 IU/kg, 3 times per week compared with the values for healthy subjects.

Linearity/non-linearity

In healthy subjects, a dose-proportional increase in serum epoetin alfa concentrations was observed after intravenous administration of 150 and 300 IU/kg, 3 times per week. Administration of single doses of 300 to 2,400 IU/kg subcutaneous epoetin alfa resulted in a linear relationship between mean C_{max} and dose and between mean AUC and dose. An inverse relationship between apparent clearance and dose was noted in healthy subjects.

In studies to explore extending the dosing interval (40,000 IU once weekly and 80,000, 100,000, and 120,000 IU biweekly), a linear but non-dose-proportional relationship was observed between mean C_{max} and dose, and between mean AUC and dose at steady state.

Pharmacokinetic/pharmacodynamic relationships

Epoetin alfa exhibits a dose-related effect on haematological parameters which is independent of route of administration.

Paediatric population

A half-life of approximately 6.2 to 8.7 hours has been reported in paediatric subjects with chronic renal failure following multiple dose intravenous administration of epoetin alfa. The pharmacokinetic profile of epoetin alfa in children and adolescents appears to be similar to that of adults.

Pharmacokinetic data in neonates is limited.

A study of 7 preterm very low birth weight neonates and 10 healthy adults given i.v. 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 healthy adults.

Renal impairment

In chronic renal failure patients, the half-life of intravenously administered epoetin alfa is slightly prolonged, approximately 5 hours, compared to healthy subjects.

5.3 Preclinical safety data

In repeated dose 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 epoetin alfa for 3 years compared to a matched control group of dialysis patients who had not been treated with epoetin alfa.

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.

Long-term carcinogenicity studies have not been carried out. Conflicting reports in the literature, based on *in vitro* findings from human tumour samples, suggest erythropoietins may play a role as tumour proliferators. This is of uncertain significance in the clinical situation.

In cell cultures of human bone marrow cells, epoetin alfa stimulates erythropoiesis specifically and does not affect leucopoiesis. Cytotoxic actions of epoetin alfa on bone marrow cells could not be detected.

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, and the significance to humans is unknown given therapeutic dose levels.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine
Sodium chloride
Sodium phosphate dibasic dihydrate
Sodium phosphate monobasic dihydrate
Polysorbate 80
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

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

For the purpose of ambulatory use, the product may be taken out of the refrigerator, without being replaced, for a maximum period of 3 days at a temperature not above 25°C. If the medicine has not been used at the end of this period, it should be disposed of.

6.5 Nature and contents of container

EPREX 4,000 IU/mL solution for injection in pre-filled syringe
0.5 mL (2,000 IU) of solution for injection in a pre-filled syringe (type I glass) with plunger (Teflon-faced rubber) and needle with a needle cover (liner contains dry natural rubber [a derivative of latex] with polypropylene cap) and a PROTECS™ needle guard device (polycarbonate) attached to the syringe - pack size of 6.

EPREX 10,000 IU/mL solution for injection in pre-filled syringe
0.3 mL (3,000 IU) of solution for injection in a pre-filled syringe (type I glass) with plunger (Teflon-faced rubber) and needle with a needle cover (liner contains dry natural rubber [a derivative of latex] with polypropylene cap) and a PROTECS™ needle guard device (polycarbonate) attached to the syringe - pack size of 6.

0.4 mL (4,000 IU) of solution for injection in a pre-filled syringe (type I glass) with plunger (Teflon- faced rubber) and needle with a needle cover (liner contains dry natural rubber [a derivative of latex] with polypropylene cap) and a PROTECS™ needle guard device (polycarbonate) attached to the syringe - pack size of 6.

0.5 mL (5,000 IU) of solution for injection in a pre-filled syringe (type I glass) with plunger (Teflon-faced rubber) and needle with a needle caver (liner contains dry natural rubber [a

derivative of latex] with polypropylene cap) and a PROTECS™ needle guard device (polycarbonate) attached to the syringe - pack size of 6.

0.6 mL (6,000 IU) of solution for injection in a pre-filled syringe (type I glass) with plunger (Teflon-faced rubber) and needle with a needle cover (liner contains dry natural rubber [a derivative of latex] with polypropylene cap) and a PROTECS™ needle guard device (polycarbonate) attached to the syringe - pack size of 6.

0.8 mL (8,000 IU) of solution for injection in a pre-filled syringe (type I glass) with plunger (Teflon-faced rubber) and needle with a needle cover (liner contains dry natural rubber [a derivative of latex] with polypropylene cap) and a PROTECS™ needle guard device (polycarbonate) attached to the syringe - pack size of 6.

1.0 mL (10,000 IU) of solution for injection in a pre-filled syringe (type I glass) with plunger (Teflon-faced rubber) and needle with a needle cover (liner contains dry natural rubber [a derivative of latex] with polypropylene cap) and a PROTECS™ needle guard device (polycarbonate) attached to the syringe - pack size of 6

<u>EPREX 40,000 IU/mL solution for injection in pre-filled syringe</u>
0.5 mL (20,000 IU) of solution for injection in a pre-filled syringe (type I glass) with plunger (Teflon- faced rubber) and needle with a needle cover (liner contains dry natural rubber [a derivative of latex] with polypropylene cap) and a PROTECS™ needle guard device (polycarbonate) attached to the syringe - pack sizes of 1,4 or 6.

0.75 mL (30,000 IU) of solution for injection in a pre-filled syringe (type I glass) with plunger (Teflon-faced rubber) and needle with a needle cover (liner contains dry natural rubber [a derivative of latex] with polypropylene cap) and a PROTECS™ needle guard device (polycarbonate) attached to the syringe - pack sizes of 1,4 or 6.

1.0 mL (40,000 IU) of solution for injection in a pre-filled syringe (type I glass) with plunger (Teflon- faced rubber) and needle with a needle cover (liner contains dry natural rubber [a derivative of latex] with polypropylene cap) and a PROTECS™ needle guard device (polycarbonate) attached to the syringe - pack sizes of 1,4 or 6.

6.6 Special precautions for disposal and other handling

The product should not be used, and discarded
- if the seal is broken,
- if the liquid is coloured or you can see particles floating in it,
- if you know, or think that it may have been accidentally frozen, or
- if there has been a refrigerator failure.

The product is for single use only. Only take one dose of EPREX from each syringe. In case only a partial dose of the syringe is required, the cover should be removed before the plunger is pushed up to the desired graduation mark to remove unwanted solution before injection. Refer to section 3. How to use EPREX (instructions on how to inject EPREX) of the package leaflet.

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

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7 Graduation marks

The syringe label contains numbered graduation marks to provide for the administration of a part of the dose (see Section 6.6). However, the product is for single use only. Only one dose of EPREX from each syringe should be taken

7 MARKETING AUTHORISATION HOLDER

J-C Health Care Ltd., Kibbutz Shefayim 6099000, Israel.

8 Manufacturer

Cilag AG, Schaffhausen, Switzerland.
HOCHSTRASSE 201 CH-8205 SCHAFFHAUSEN, SWITZERLAND

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