Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

EPREX 2,000 IU/mL solution for injection in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Epoetin alfa 2,000 IU/mL (16.8 micrograms per mL), produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology

A pre-filled syringe of 0.5 mL contains 1,000 IU (8.4 micrograms) of epoetin alfa.

Excipient(s) with known effect
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially "sodium free."

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe.

Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

EPREX is indicated for the treatment of symptomatic anaemia associated with chronic renal failure (CRF):
- in adults and paediatrics aged 1 to 18 years on haemodialysis and adult patients on peritoneal dialysis.
- in adults with renal insufficiency not yet undergoing dialysis for the treatment of severe anaemia of renal origin accompanied by clinical symptoms in patients.

EPREX is indicated in adults receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma, and at risk of transfusion as assessed by the patient's general status (e.g. cardiovascular status, pre-existing anaemia at the start of chemotherapy) for the treatment of anaemia and reduction of transfusion requirements.

EPREX is indicated in adults in a predonation programme to increase the yield of autologous blood. Treatment should only be given to patients with moderate anaemia (haemoglobin concentration range between 10 to 13 g/dL [6.2 to 8.1 mmol/L], no iron deficiency) if blood saving procedures are not available or insufficient when the scheduled major elective surgery requires a large volume of blood (4 or more units of blood for females or 5 or more units for males).

EPREX is indicated for non-iron deficient adults prior to major elective orthopaedic surgery having a high perceived risk for transfusion complications to reduce exposure to allogeneic blood transfusions. Use should be restricted to patients with moderate anaemia (e.g. haemoglobin concentration range between 10 to 13 g/dL) who do not have an autologous predonation programme available and with expected moderate blood loss (900 to 1,800 mL).

EPREX is indicated for the treatment of symptomatic anaemia (haemoglobin concentration of ≤ 10 g/dL) in adults with low- or intermediate-1-risk primary myelodysplastic syndromes (MDS) who have low serum erythropoietin (<200 mU/mL).

4.2 Posology and method of administration

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 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 concentration range may be observed. Haemoglobin variability should be addressed through dose management, with consideration for the haemoglobin concentration 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).

Treatment with EPREX is divided into two stages – correction and maintenance phase.

Adult haemodialysis patients

In 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, 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).

Patients with very low initial haemoglobin (< 6 g/dL or < 3.75 mmol/L)may require higher maintenance doses than patients whose initial anaemia is less severe (> 8 g/dL or > 5 mmol/L).

Adult patients with renal insufficiency not yet undergoing dialysis

Where intravenous access is not readily available EPREX may be administered subcutaneously.

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: haemoglobin between 10 g/dL and 12 g/dL (6.2 to 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.

Correction phase

The starting dose is 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 adult 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 to patients with anaemia (e.g. haemoglobin concentration ≤ 10 g/dL (6.2 mmol/L)).

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

Alternatively, EPREX can be administered at an initial dose of 450 IU/kg subcutaneously once weekly.

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

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

If the haemoglobin concentration has increased by at least 1 g/dL (0.62 mmol/L) or the reticulocyte count has increased ≥ 40,000 cells/microlitre above baseline after 4 weeks of treatment, the dose should remain at 150 IU/kg 3 times per week or 450 IU/kg once weekly.

If the haemoglobin concentration increase is < 1 g/dL (< 0.62 mmol/L) and the reticulocyte count has increased < 40,000 cells/microlitre above baseline, increase the dose to 300 IU/kg 3 times per week. If after an additional 4 weeks of therapy at 300 IU/kg 3 times per week, the haemoglobin concentration has increased ≥ 1 g/dL (≥ 0.62 mmol/L) or the reticulocyte count has increased ≥ 40,000 cells/microlitre, the dose should remain at 300 IU/kg 3 times per week.

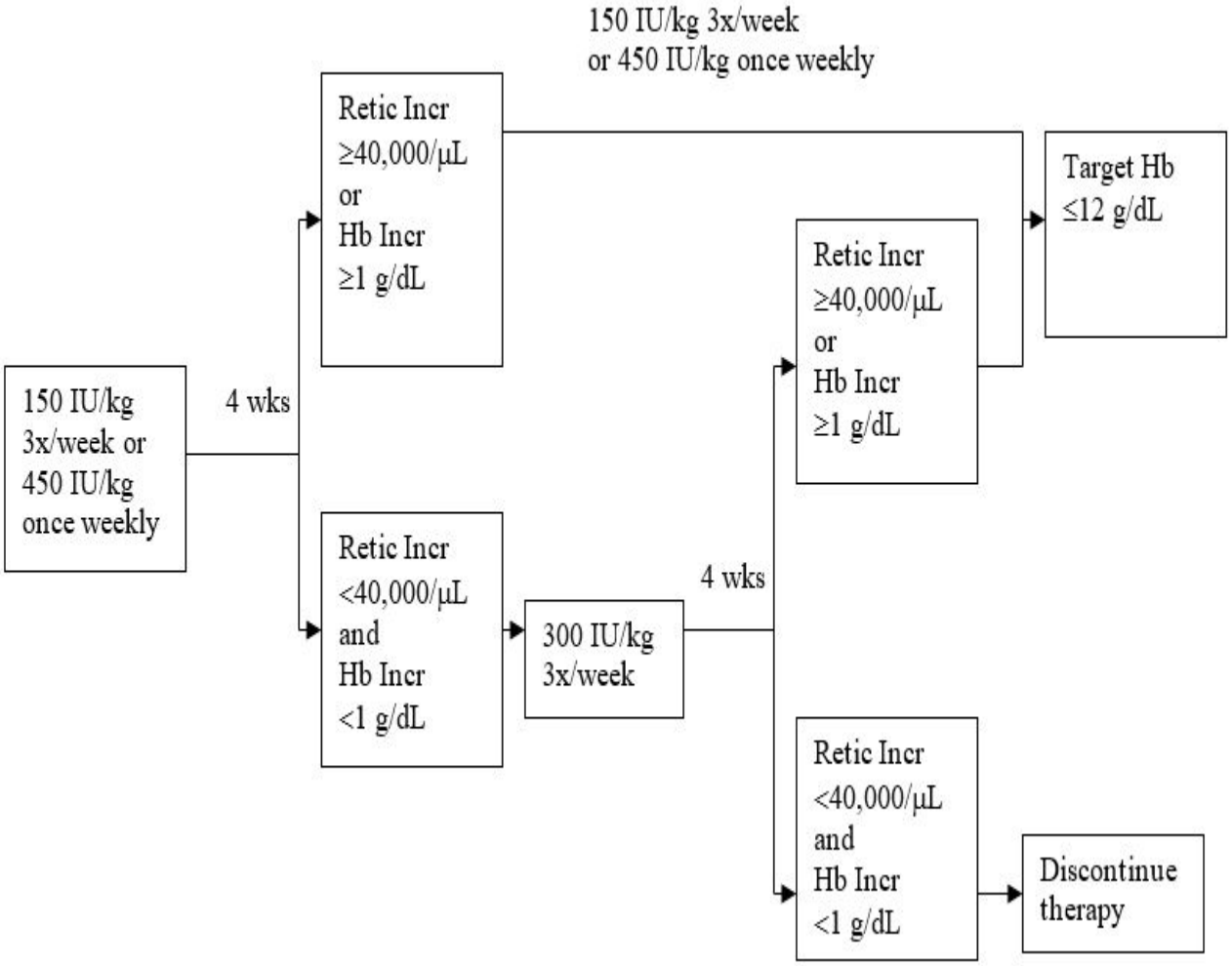
If the haemoglobin concentration has increased < 1 g/dL (< 0.62 mmol/L) and the reticulocyte count has increased < 40,000 cells/microlitre above baseline, response is unlikely and treatment should be discontinued.

Dose adjustment to maintain haemoglobin concentrations between 10 g/dL to 12 g/dL

If the haemoglobin concentration is increasing by more than 2 g/dL (1.25 mmol/L) per month, or if the haemoglobin concentration level exceeds 12 g/dL (7.5 mmol/L), reduce the EPREX dose by about 25 to 50%.

If the haemoglobin concentration level exceeds 13 g/dL (8.1 mmol/L), discontinue therapy until it falls below 12 g/dL (7.5 mmol/L) and then reinitiate EPREX therapy at a dose 25% below the previous dose.

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.

EPREX therapy should continue until one month after the end of chemotherapy.

Treatment of adult surgery patients in an autologous predonation programme

Mildly anaemic patients (haematocrit of 33 to 39%) requiring predeposit of ≥ 4 units of blood should be treated with EPREX 600 IU/kg intravenously, 2 times per week for 3 weeks prior to surgery. EPREX should be administered after the completion of the blood donation procedure.

Treatment of adult patients scheduled for major elective orthopaedic surgery

The recommended dose is EPREX 600 IU/kg administered subcutaneously 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, EPREX 300 IU/kg should be administered subcutaneously daily for 10 consecutive days prior to surgery, on the day of surgery and for four days immediately thereafter.

If the haemoglobin level reaches 15 g/dL, or higher, during the preoperative period, administration of EPREX should be stopped and further dosages should not be administered.

Treatment of adult patientswith low- or intermediate-1-risk MDS

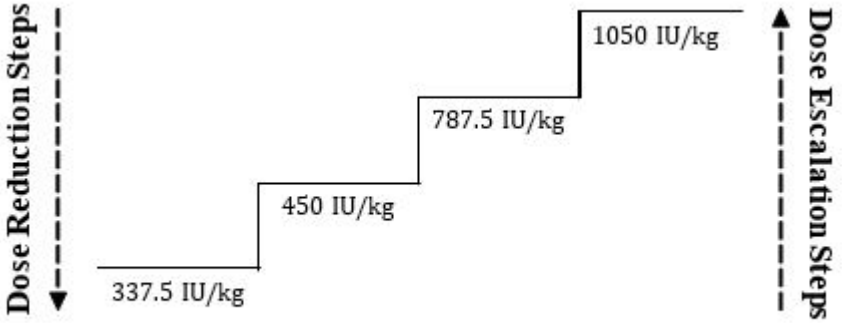
EPREX should be administered to patients with symptomatic anaemia (e.g. haemoglobin concentration ≤10 g/dL (6.2 mmol/L)).

The recommended starting dose is EPREX 450 IU/kg (maximum total dose is 40,000 IU) administered subcutaneously once every week, with not less than 5 days between doses.

Appropriate dose adjustments should be made to maintain haemoglobin concentrations within the target range of 10 g/dL to 12 g/dL (6.2 to 7.5 mmol/L). It is recommended that initial erythroid response be assessed 8 to 12 weeks following initiation of treatment. Dose increases and decreases should be done one dosing step at a time (see diagram below). A haemoglobin concentration of greater than 12 g/dL (7.5 mmol/L) should be avoided.

Dose increase: Dose should not be increased over the maximum of 1050 IU/kg (total dose 80,000 IU) per week. If the patient loses response or haemoglobin concentration drops by ≥1 g/dL upon dose reduction the dose should be increased by one dosing step. A minimum of 4 weeks should elapse between dose increases.

*Dose hold and decrease:*Epoetin alfa should be withheld when the haemoglobin concentration exceeds 12 g/dL (7.5 mmol/L). Once the haemoglobin level is <11 g/dL the dose can be restarted on the same dosing step or one dosing step down based on physician judgement. Decreasing the dose by one dosing step should be considered if there is a rapid increase in haemoglobin (> 2 g/dL over 4 weeks).



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.

Paediatric population

Treatment of symptomatic anaemia in chronic renal failure patients on haemodialysis

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 haemoglobin concentration range is between 9.5 g/dL to 11 g/dL (5.9 to 6.8 mmol/L). EPREX should be administered in order to increase haemoglobin to not greater than 11 g/dL (6.8 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.

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.

Treatment with EPREX is divided into two stages – correction and maintenance phase.

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 haemoglobin levels within the desired concentration range between 9.5 g/dL to 11 g/dL (5.9 to 6.8 mmol/L).

Generally, children under 30 kg require higher maintenance doses than children over 30 kg and adults.
Paediatric patients with very low initial haemoglobin (< 6.8 g/dL or < 4.25 mmol/L) may require higher maintenance doses than patients whose initial haemoglobin is higher (> 6.8 g/dL or > 4.25 mmol/L).

Anaemia in chronic renal failure patients before initiation of dialysis or on peritoneal dialysis

The safety and efficacy of EPREX in chronic renal failure patients with anaemia before initiation of dialysis or on peritoneal dialysis have not been established. Currently available data for subcutaneous use of EPREX in these populations are described in section 5.1 but no recommendation on posology can be made.

Treatment of paediatric patients with chemotherapy-induced anaemia

The safety and efficacy of EPREX in paediatric patients receiving chemotherapy have not been established (see section 5.1).

Treatment of paediatric surgery patients in an autologous predonation programme

The safety and efficacy of EPREX in paediatrics have not been established. No data are available.

Treatment of paediatric patients scheduled for major elective orthopaedic surgery

The safety and efficacy of EPREX in paediatrics have not been established. No data are available.

Method of administration

Precautions to be taken before handling or administering the medicinal product.

Before use, leave the EPREX syringe to stand until it reaches room temperature. This usually takes between 15 and 30 minutes.

Treatment of symptomatic anaemia in adult chronic renal failure patients

In patients with chronic renal failure where intravenous access is routinely available (haemodialysis patients) administration of EPREX by the intravenous route is preferable.

Where intravenous access is not readily available (patients not yet undergoing dialysis and peritoneal dialysis patients) EPREX may be administered as a subcutaneous injection.

Treatment of adult patients with chemotherapy-induced anaemia

EPREX should be administered as a subcutaneous injection.

Treatment of adult surgery patients in an autologous predonation programme

EPREX should be administered by the intravenous route.

Treatment of adult patients scheduled for major elective orthopaedic surgery

EPREX should be administered as a subcutaneous injection.

Treatment of adult patientswith low- or intermediate-1-risk MDS

EPREX should be administered as a subcutaneous injection.

Treatment of symptomatic anaemia in paediatric chronic renal failure patients on haemodialysis

In paediatric patients with chronic renal failure where intravenous access is routinely available (haemodialysis patients) administration of EPREX by the intravenous route is preferable.

Intravenous administration

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 (see Posology, ***Adult haemodialysis patients***).

A slower administration 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 administration

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 should be 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 themselves, instruction as to the proper dosage and administration should be provided.

As with any other injectable product, check that there are no particles in the solution or change in colour.

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.

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

<u>General</u>

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

In order to improve the traceability of erythropoiesis-stimulating agents (ESAs), the trade name and the batch number of the

administered ESA should be clearly recorded (or stated) in the patient file.

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 therate 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 levelhas 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.

4.5 Interaction with other medicinal products and other forms of interactions

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 randomized, 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, and 102 exposed subjects in 2 MDS studies. Adverse drug reactions reported by [3]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], Thrombocythemia	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.

Adult patientswith low- or intermediate-1-risk MDS

In the randomized, double-blind, placebo-controlled, multicenter study 4 (4.7%) subjects experienced TVEs (sudden death, ischemic stroke, embolism, and phlebitis). All TVEs occurred in the epoetin alfa group and in the first 24 weeks of the study. Three were confirmed TVE and in the remaining case (sudden death), the thromboembolic event was not confirmed. Two subjects had significant risk factors (atrial fibrillation, heart failure and thrombophlebitis).

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 authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
E-mail: medsafety@hpra.ie

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 randomized 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 hospitalization for congestive heart failure) occurred among 125 (18%) of the 715 patients in the higher haemoglobin group compared to 97 (14%) among the 717 patients in the lower haemoglobin group (hazard ratio [HR] 1.3, 95% CI: 1.0, 1.7, $p = 0.03$).

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 tumors, 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/microlitre.

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).

Treatment of adult patientswith low- or intermediate-1-risk MDS

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

Subjects were stratified by serum erythropoetin (sEPO) level and prior transfusion status at screening. Key baseline characteristics for the <200 mU/mL stratum are shown in the table below.

Baseline Characteristics for Subjects with sEPO<200mU/mL at Screening		
	Randomized	
	Epoetin alfa	Placebo
Total (N)[b]	85[a]	45
Screening sEPO <200 mU/mL (N)	71	39
Hemoglobin (g/L)		
N	71	39
Mean	92.1 (8.57)	92.1 (8.51)
Median	94.0	96.0
Range	(71, 109)	(69, 105)
95% CI for mean	(90.1, 94.1)	(89.3, 94.9)
Prior Transfusions		
N	71	39
Yes	31 (43.7%)	17 (43.6%)
≤ 2 RBC Units	16 (51.6%)	9 (52.9%)
>2 and ≤4 RBC Units	14 (45.2%)	8 (47.1%)
>4 RBC Units	1 (3.2%)	0
No	40 (56.3%)	22 (56.4%)

[a] one subject did not have sEPO data
[b] in the ≥200 mU/mL stratum there were 13 subjects in the epoetin alfa group and 6 subjects in the placebo group

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

Erythroid response during the first 24 weeks of the study was demonstrated by 27/85 (31.8%) of the subjects in the epoetin alfa group compared to 2/45 (4.4%) of the subjects in the placebo group (p<0.001). All of the responding subjects were in the stratum with sEPO <200 mU/mL during screening. In that stratum, 20/40 (50%) subjects without prior transfusions demonstrated erythroid response during the first 24 weeks, compared with 7/31 (22.6%) subjects with prior transfusions (two subjects with prior transfusion reached primary endpoint based on reduction of RBC units transfused by an absolute number of at least 4 units every 8 weeks compared to the 8 weeks prior to baseline).

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

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

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

6.2 Incompatibilities

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

6.3 Shelf life

18 months.

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

0.5 mL (1,000 IU) of solution for injection in a pre-filled syringe (type I glass) with plunger (Teflon-faced rubber) and needle with a needle shield (rubber with polypropylene cover) and a PROTECS™ needle guard device (polycarbonate) attached to the syringe - pack size of 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 numbered 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.

7 MARKETING AUTHORISATION HOLDER

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