Binocrit ®
Epoetin alfa

1. NAME OF THE MEDICINAL PRODUCT

Binocrit solution for injection in a pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

a) Binocrit 2,000 IU/1 ml solution for injection in a pre-filled syringe:
Each ml of solution contains 2,000 IU of epoetin alfa* corresponding to 16.8 micrograms per ml
1 pre-filled syringe of 1 ml contains 2,000 international units (IU) corresponding to 16.8 micrograms epoetin alfa

b) Binocrit 4,000 IU/0.4 ml solution for injection in a pre-filled syringe:
Each ml of solution contains 10,000 IU of epoetin alfa* corresponding to 84.0 micrograms per ml
1 pre-filled syringe of 0.4 ml contains 4,000 international units (IU) corresponding to 33.6 micrograms epoetin alfa

c) Binocrit 10,000 IU/1 ml solution for injection in a pre-filled syringe:
Each ml of solution contains 10,000 IU of epoetin alfa* corresponding to 84.0 micrograms per ml
1 pre-filled syringe of 1 ml contains 10,000 international units (IU) corresponding to 84.0 micrograms epoetin alfa

d) Binocrit 40,000 IU/1 ml solution for injection in a pre-filled syringe:
Each ml of solution contains 40,000 IU of epoetin alfa* corresponding to 336.0 micrograms per ml
1 pre-filled syringe of 1 ml contains 40,000 international units (IU) corresponding to 336.0 micrograms epoetin alfa

* Produced in CHO cell line by recombinant DNA technology

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in a pre-filled syringe (injection).
Clear colourless solution.

Binocrit is a biosimilar medicinal product of Eprex.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of anemia associated with chronic renal failure in adult hemodialysis, peritoneal dialysis and predialysis patients and pediatric patients on hemodialysis.
- Treatment of anemia and reduction of transfusion in adult cancer patients with non-myeloid malignancies receiving chemotherapy.
- To facilitate autologous blood collection within a predeposit program and decrease the risk of receiving allogeneic blood transfusions in patients with hematocrits of 33 - 39%, who are scheduled for major elective surgery and are expected to require more blood than that which can be obtained through autologous blood collection techniques in the absence of Binocrit.
- Binocrit is indicated in adult patients with mild to moderate anemia (hemoglobin > 10 to ≤ 13 g/dL) scheduled for elective surgery with an expected moderate blood loss (2 - 4 units or 900 to 1800 mL) to reduce exposure to allogeneic blood transfusions and to facilitate erythropoietic recovery).
- Binocrit is indicated for the treatment of 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

Binocrit may be administered by intravenous or subcutaneous injection.

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

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

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

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

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

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

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

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

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

In situations where the physician determines that a patient or caregiver can safely and effectively

administer Binocrit subcutaneously, instruction as to the proper dosage and administration should be provided.

Dosage

Chronic Renal Failure Patients

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

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

In patients with chronic renal failure, maintenance hemoglobin concentration should not exceed the upper limit of the hemoglobin concentration range (see Warnings and Precautions, Renal Failure Patients).

When changing the route of administration, the same dose should be used initially and then titrated to keep hemoglobin in the hemoglobin concentration range.

In the correction phase, the dose of Binocrit should be increased if the hemoglobin does not increase at least 1 g/dL (0.62 mmol/L) per month.

A clinically significant increase in hemoglobin is usually not observed in less than 2 weeks and may require up to 6 - 10 weeks in some patients.

When the hemoglobin concentration is within range, the dose should be decreased by 25 IU/kg/dose in order to avoid exceeding the hemoglobin concentration range. Dose should be reduced when hemoglobin approaches 12 g/dL.

Dose reductions may be made by omitting one of the weekly doses or by decreasing the amount of each dose.

Adult Hemodialysis Patients

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

The treatment is divided into two stages:

Correction Phase

50 IU/kg three times per week.

When necessary, dose adjustments should be made in increments of 25 IU/kg three times per week at intervals of at least 4 weeks until the hemoglobin concentration range (10 - 12 g/dL [6.2-7.5 mmol/L]) is achieved.

Maintenance Phase

Adjust dosage in order to maintain hemoglobin values at the desired level: Hb between 10 and 12 g/dL

(6.2 – 7.5 mmol/L).

The maintenance dose should be individualized for each chronic renal failure patient. The recommended total weekly dose is between 75 and 300 IU/kg.

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

Pediatric Hemodialysis Patients
The treatment is divided into two stages:

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

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

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

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

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

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

Adult Peritoneal Dialysis Patients
In peritoneal dialysis patients, where intravenous access is not readily available, Binocrit may be administered subcutaneously.

The treatment is divided into two stages:

Correction Phase
50 IU/kg twice per week.

When necessary, dose adjustments should be made in increments of 25 IU/kg twice per week at intervals of at least 4 weeks until the hemoglobin concentration range (10 - 12 g/dL [6.2-7.5 mmol/L]) is achieved.

Maintenance Phase
The usual dose to maintain the hemoglobin concentration range (10 - 12 g/dL [6.2-7.5 mmol/L]) is between 25 and 50 IU/kg twice per week in two equal injections.

Adult Predialysis Patients (Adult Patients With End Stage Renal Insufficiency)
In patients with renal insufficiency not yet undergoing dialysis, where intravenous access is not readily available, Binocrit may be administered subcutaneously. The treatment is divided into two stages:

Correction Phase
50 IU/kg three times per week.

When necessary, dose adjustments should be made in increments of 25 IU/kg three times per week at intervals of at least 4 weeks until the hemoglobin concentration range (10-12 g/dL [6.2-7.5 mmol/L]) is achieved.

Maintenance Phase
The usual dose to maintain the hemoglobin concentration range is between 17 and 33 IU/kg three times per week.

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

Cancer Patients
Adult Cancer Patients
The subcutaneous route of administration should be used.

The hemoglobin concentration range should be 10 to 12 g/dL (7.5 mmol/L) in men and women and it should not be exceeded.

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

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

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

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

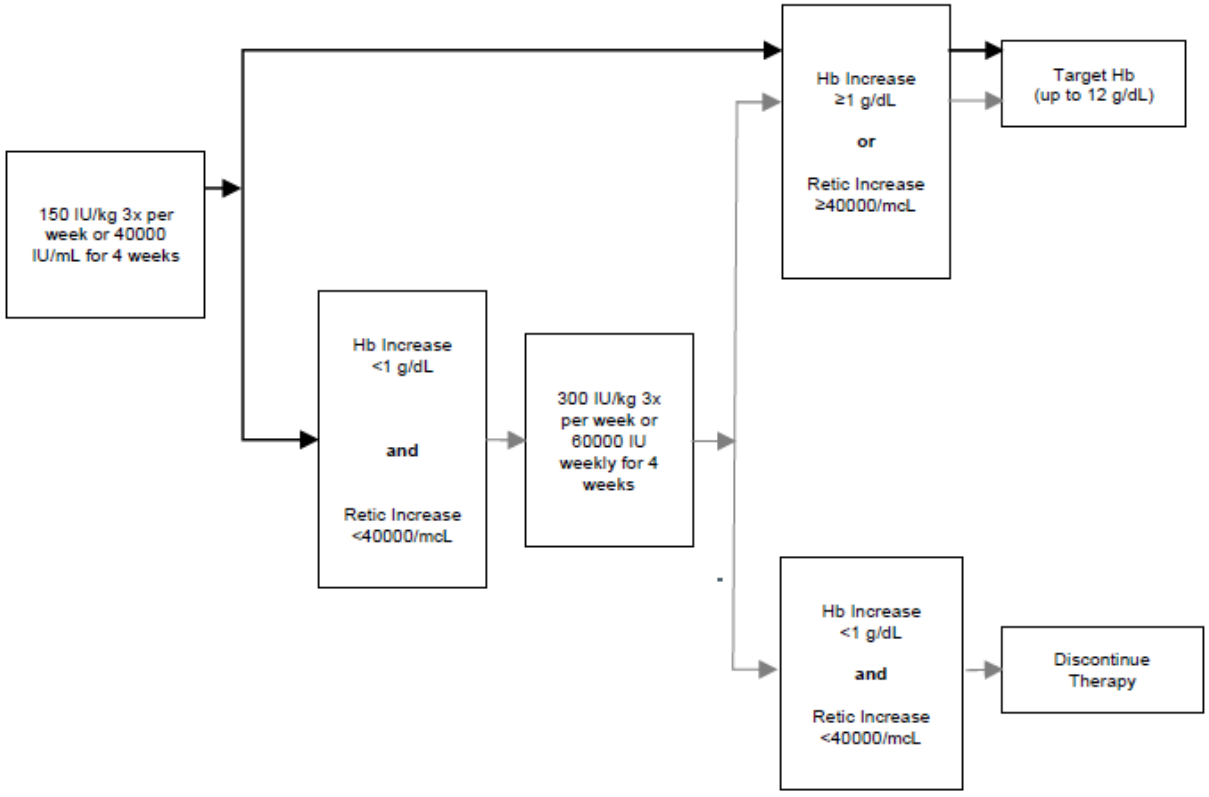
If after 4 weeks of treatment at the initial dose, the hemoglobin has not increased by ≥ 1 g/dL (0.6 mmol/L) and the reticulocyte count has not increased by ≥ 40,000 cells/mcL above baseline, in the absence of red blood cell transfusion, the dose should be increased to 300 IU/kg 3 times per week or 60,000 IU weekly.

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

cells/mcL the dose should remain unchanged.

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

The recommended dosing regimen is described in the following diagram:



A rate of rise in hemoglobin of greater than 1 g/dL (0.6 mmol/L) per 2 week or 2 g/dL (1.25 mmol/L) per month or hemoglobin levels of > 12 g/dL (> 8.1 mmol/L) should be avoided. If the hemoglobin is rising by more than 1 g/dL (0.6 mmol/L) per two week or 2 g/dL (1.25 mmol/L) per month or hemoglobin is approaching 12 g/dL (7.5 mmol/L), reduce the Binocrit dose by about 25 - 50% depending upon the rate of rise of hemoglobin. If the hemoglobin exceeds 12 g/dL (7.5 mmol/L), withhold therapy until it falls below 12 g/dL (7.5 mmol/L) and then reinitiate Binocrit therapy at a dose 25% below the previous dose.

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

Mildly anemic patients (hematocrit of 33 to 39% and/or hemoglobin 10 to 13 g/dL (6.2-8.1 mmol/L) requiring predeposit of ≥ 4 units of blood, should be treated with Binocrit at 600 IU/kg 2 times weekly for 3 weeks prior to surgery.

For those patients who require a lesser degree of erythropoietic stimulation, a dose regimen of 150 - 300 IU/kg administered twice weekly has been shown to augment autologous pre-donation and to decrease the subsequent decline in hematocrit.

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

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

In cases where there is a medical need to reduce the time before surgery to less than three weeks, the recommended dose regimen is 300 IU/kg for 10 consecutive days before surgery, on the day of surgery and up to 4 days after surgery. 300 IU/kg/day is recommended for hemoglobin levels ≤ 13 g/dL (8.1 mmol/L). If the hemoglobin level reaches 15 g/dL, or higher, administration of Binocrit should be stopped and further doses should not be given.

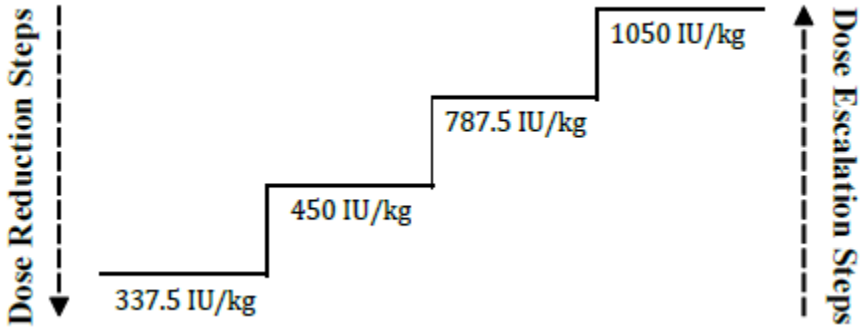
Adult Patients with low- or intermediate-1-risk MDS
The subcutaneous route of administration should be used.

Binocrit should be administered to low- or intermediate-1- risk MDS patients with anemia (e.g. hemoglobin concentration ⩽ 10 g/dL (6.2 mmol/L)).

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

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

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



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

Special populations

Pediatrics (17 years of age and younger)

Treatment of pediatric patients with chemotherapy-induced anemia

The safety and efficacy of Binocrit in pediatric patients receiving chemotherapy have not been established.

Treatment of pediatric surgery patients in an autologous predonation program

The safety and efficacy of Binocrit in pediatric surgery patients in an autologous predonation program have not been established.

Treatment of pediatric patients scheduled for major elective orthopedic surgery

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

Elderly (65 years of age and older)

Dose selection and adjustment for an elderly patient should be individualized to achieve and maintain the hemoglobin concentration range.

4.3 Contraindications

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

- Patients who develop Pure Red Cell Aplasia (PRCA) following treatment with any erythropoietin should not receive Binocrit 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 Binocrit.

The use of Binocrit 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 arteria, 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

Hypertension
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.

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

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

General
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 and chronic liver failure. The safety of epoetin alfa has not been established in patients with hepatic dysfunction. Due to decreased metabolism, patients with hepatic dysfunction may have increased erythropoiesis with epoetin alfa.

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 risks 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.

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

The safety and efficacy of epoetin alfa therapy have not been established in patients with underlying hematologic diseases (e.g., hemolytic anemia, sickle cell anemia, thalassemia).

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.

Other causes of anaemia (iron, folate or vitamin B_{12} deficiency, aluminum 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 100ng/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.

Blistering and skin exfoliation reactions including erythema multiforme and Stevens-Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN), have been reported in a small number of patients

treated with epoetin alfa. Discontinue epoetin alfa therapy immediately if a severe cutaneous reaction, such as SJS/TEN, is suspected.

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

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

Geriatric Use
No overall differences in safety or effectiveness were observed between geriatric and younger patients. The dose requirements for epoetin alfa in geriatric and younger patients within the 4 studies using the three times per week schedule were similar. Insufficient numbers of patients were enrolled in the study using the weekly dosing regimen to determine whether the dosing requirements differ for this schedule.

No differences in safety or effectiveness were observed between geriatric and younger patients. Dose selection and adjustment for an elderly patient should be individualized to achieve and maintain the hemoglobin concentration range (see Section 4.2).

Insufficient numbers of patients age 65 or older were enrolled in clinical studies for the treatment of anemia associated with pre-dialysis chronic renal failure, cancer chemotherapy, and Zidovudine-treatment of HIV infection to determine whether they respond differently from younger subjects.

Renal Failure Patients
Treatment of symptomatic anemia in adult and pediatric chronic renal failure patients:

Chronic renal failure patients being treated with epoetin alfa should have hemoglobin 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 hemoglobin should be approximately 1 g/dL(0.62 mmol/L)/per month and should not exceed 2 g/dL (1.2 mmol/L)/per month to minimize risks of an increase in hypertension. Dose should be reduced when hemoglobin approaches 12 g/dL.

In patients with chronic renal failure, maintenance hemoglobin concentration should not exceed the upper limit of the hemoglobin concentration range as recommended under Section 4.2. Hemoglobin levels targeted to 13 g/dL or higher may be associated with a higher risk of cardiovascular events, including death.

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

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

Shunt thromboses have occurred in hemodialysis patients, especially in those who have a tendency to hypotension or whose arteriovenous fistula exhibit complications (e.g., stenoses, aneurisms, etc.) Early

shunt revision and thrombosis prophylaxis by administration of acetylsalicylic acid, for example, is recommended in these patients.

Hyperkalemia 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 the appropriate treatment of the hyperkalemia, consideration should be given to ceasing epoetin alfa administration until the serum potassium level has been corrected.

As a result of an increase in packed cell volume, hemodialysis patients receiving epoetin alfa frequently require an increase in heparin dose during dialysis. If heparinization is not optimal, occlusion of the dialysis system is possible.

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

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

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

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

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

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

HIV-Infected Patients
If HIV-infected patients fail to respond or maintain a response to epoetin alfa, other etiologies including

iron deficiency anemia should be considered and evaluated.

Adult Surgery Patients in Autologous Predonation Programmes
All special warnings and precautions associated with autologous predonation programmes, especially routine volume replacement, should be respected in patients being supplemented with epoetin alfa.

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

Patients scheduled for major elective orthopedic 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 hemoglobin of > 13 g/dL(8.1 mmol/L), the possibility that epoetin alfa treatment may be associated with an increased risk of postoperative thrombotic/vascular events cannot be excluded. Therefore, it should not be used in patients with baseline hemoglobin > 13 g/dL (8.1 mmol/L).

The use of epoetin alfa is not recommended in perisurgery patients with a baseline hemoglobin of > 13 g/dL (8.1 mmol/L).

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per pre-filled syringe, i.e. essentially "sodium-free".

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 medicinal products. Drugs that decrease erythropoiesis may decrease the response to epoetin alfa.

Since cyclosporin is bound by red blood cells (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 granulocyte colony- stimulating factor (G-CSF) or granulocyte macrophage colony-stimulating factor (GM-CSF) with regard to haematological differentiation or proliferation of tumour cells from biopsy specimens *in vitro*.

The effect of epoetin alfa may be potentiated by the simultaneous therapeutic administration of a hematinic agent, such as ferrous sulphate, when a deficiency state exists.

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

4.6 Pregnancy and lactation

Pregnancy

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

There are no adequate and well-controlled studies in pregnant women. epoetin alfa should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

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

Fertility
The effect of epoetin alfa on human fertility has not been studied.

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 the 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.

Hypersensitivity reactions, including cases of rash, (including urticaria, anaphylactic reaction, and angioedema have been reported.

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.

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 3714 subjects in 29 randomised, double-blinded, placebo or standard of care (SOC) controlled studies, the overall safety profile of epoetin alfa was evaluated in-2238 anaemic subjects. Included were 228 epoetin alfa-treated CRF subjects in 4 chronic renal failure studies (2 studies in pre-dialysis, N=131

exposed CRF subjects not yet on dialysis-and 2 in dialysis N=97 exposed CRF subjects); 1404 exposed cancer subjects in 16 studies of anaemia due to chemotherapy; 144 exposed subjects in 4 HIV-infection studies; 147 exposed subjects in 2 studies of autologous blood donation; and 213 exposed subjects in 1 study in the perisurgical setting, and 102 exposed subjects in 2 studies in MDS. Adverse drug reactions reported by ≥1% of subjects treated with epoetin alfa in these trials are shown 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).

Blood and lymphatic system disorders
Rare: Pure red cell aplasia[3], thrombocythaemia

Immune system disorders
Uncommon: Hypersensitivity[3]
Rare: Anaphylactic reaction[3]

Metabolism and nutrition disorders
Uncommon: Hyperkalaemia[1]

Nervous system disorders
Common: Headache
Uncommon: Convulsions

Vascular disorders
Common: Venous and arterial thromboses[2], hypertension
Not known: Hypertensive crisis[3]

Respiratory, thoracic, and mediastinal disorders
Common: Cough
Uncommon: Respiratory tract congestion
Not known: Pulmonary arterial hypertension (class label for interferon products). Cases of pulmonary arterial hypertension (PAH) have been reported with interferon alfa products, notably in patients with risk factors for PAH (such as portal hypertension, HIV infection, cirrhosis). Event were reported at various time points typically several months after starting treatment with interferon alfa.[4]

Gastrointestinal disorders
Very common: Diarrhoea, nausea, vomiting

Skin and subcutaneous tissue disorders
Common: Rash
Uncommon: Urticaria[3]
Not known: Angioneurotic oedema[3]

Musculoskeletal and connective tissue disorders
Common: Arthralgia, bone pain, myalgia, pain in extremity

Congenital, familial and genetic disorders
Rare: Porphyria acute[3]

General disorders and administration site conditions

Very common:	Pyrexia
Common:	Chills, influenza-like illness, injection site reaction, oedema peripheral
Not known:	Medicinal product ineffective[3]

Investigations

Rare:	Anti-erythropoeitin antibody positive

[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.
[4] Directive from National Pharmaceutical Regulatory Agency (15 Feb 2017)

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

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).

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 epoetin alfa (see section 4.4). More cases have been reported with subcutaneous (SC) route of administration, compared with the IV route.

Adult patients with low- or intermediate-1-risk MDS
In the randomised, double-blind, placebo-controlled, multicenter study 4 (4.7%) subjects experienced TVEs (sudden death, ischaemic 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.

4.9 Overdose

The therapeutic margin of epoetin alfa is very wide. Overdose 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: other antianaemic preparations, 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.

Pharmacodynamic effects
Pharmacodynamic responses to HSA-free Epoetin alfa, change in percent reticulocytes, hemoglobin, and total red blood cell counts as well as the area under the curve (AUCs) of these pharmacodynamic parameters, were similar between two dosing regimens (150 IU/kg SC 3 times per week to 40000 IU/mL SC once weekly).

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.

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.

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.

A randomised prospective trial (CHOIR) evaluated 1432 anaemic chronic renal failure patients who were not undergoing dialysis. Patients were assigned to epoetin alfa treatment targeting a maintenance haemoglobin level of 13.5 g/dl (higher than the recommended 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).

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 1000 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).

A randomised, open-label, multicentre study was conducted in 2098 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 SOC as compared with SOC alone. The median progression free survival (PFS) per investigator assessment of disease progression was 7.4 months in each arm (HR 1.09, 95% CI: 0.99, 1.20), indicating the study objective was not met. Median PFS with disease progression assessed by the Independent Review Committee was 7.6 months in each arm (HR 1.03, 95% CI: 0.92, 1.15). At clinical cutoff, 1337 deaths were reported. Median overall survival in the epoetin alfa plus SOC group was 17.2 months compared with 17.4 months in the SOC alone group (HR 1.06, 95% CI: 0.95, 1.18). Significantly fewer patients received RBC transfusions in the epoetin alfa plus SOC arm (5.8% versus 11.4%); however, significantly more patients had thrombotic vascular events in the epoetin alfa plus SOC arm (2.8% versus 1.4%). At the final analysis, 1653 deaths were reported. Median overall survival in the epoetin alfa plus SOC group was 17.8 months compared with 18.0 months in the SOC alone group (HR 1.07, 95% CI: 0.97, 1.18). The median time to progression (TTP) based on investigator-determined progressive disease (PD) was 7.5 months in the epoetin alfa plus SOC group and 7.5 months in the SOC group (HR 1.099, 95% CI: 0.998, 1.210). The median TTP based on IRC-determined PD was 8.0 months in the epoetin alfa plus SOC group and 8.3 months in the SOC group (HR 1.033, 95% CI: 0.924, 1.156).

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

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).

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

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 ($p<0.001$).

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).

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 Cmax 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 Cmax and dose, and between mean AUC and dose at steady state.

PK/PD 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

Sodium dihydrogen phosphate dihydrate
Disodium phosphate dehydrate
Sodium chloride
Glycine
Polysorbate 80
Water for injections
Hydrochloric acid (for pH-adjustment)
Sodium hydroxide (for pH-adjustment)

6.2 Incompatibilities

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

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store and transport refrigerated (2°C-8°C). This temperature range should be closely maintained until administration to the patient.
For the purpose of ambulatory use, the medicinal 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 medicinal product has not been used at the end of this period, it should be disposed of.

Do not freeze or shake.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

Pre-filled syringes (glass type I), with or without a needle safety guard, with plunger stopper (Teflon-faced rubber) sealed in a blister.

The syringes contain 1 ml (2,000 IU), 0.4 ml (4,000 IU), 1 ml (10,000 IU) or 1 ml (40,000 IU) of solution.

Pack of 1 or 6 syringes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

The pre-filled syringes are ready to use (see section 4.2). The pre-filled syringe should not be shaken. Syringes are embossed with graduation rings in order to enable partial use if required. Each graduation ring corresponds to a volume of 0.1 ml. The product is for single use only. Only take one dose of Binocrit from each syringe discarding unwanted solution before injection.

Using the pre-filled syringe with a needle safety guard
The needle safety guard covers the needle after injection to prevent needle stick injury. This does not affect normal operation of the syringe. Depress the plunger slowly and evenly until the entire dose has been given and the plunger cannot be depressed any further. While maintaining pressure on the plunger, remove the syringe from the patient. The needle safety guard will cover the needle when releasing the plunger.

Using the pre-filled syringe without a needle safety guard
Administer the dose as per standard protocol.

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

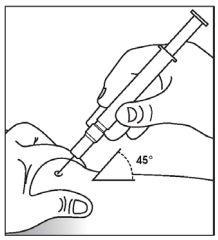
Instructions on how to inject yourself (for patients with symptomatic anaemia caused by kidney disease, for adult patients receiving chemotherapy, adult patients scheduled for orthopaedic surgery, or adult patients with myelodysplastic syndromes only)

This section contains information on how to give yourself an injection of Binocrit. **It is important that you do not try to give yourself the injection unless you have received special training from your doctor or nurse.** Binocrit is provided with or without a needle safety guard and you will be shown how to use this by your doctor or nurse. If you are not sure about giving the injection or you have any questions, please ask your doctor or nurse for help.

WARNING: Do not use if the syringe has been dropped onto a hard surface or dropped after removing the needle cap. Do not use the Binocrit prefilled syringe if it is broken. Return the prefilled syringe and the package it came in to the pharmacy.

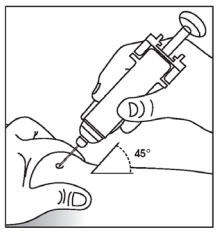
1. Wash your hands.
2. Remove one syringe from the pack and remove the protective cap from the injection needle. Syringes are embossed with graduation rings in order to enable partial use if required. Each graduation ring corresponds to a volume of 0.1 mL. If partial use of a syringe is required, remove unwanted solution before injection.
3. Clean the skin at the injection site using an alcohol wipe.
4. Form a skin fold by pinching the skin between thumb and forefinger.
5. Insert the needle into the skin fold with a quick, firm action. Inject the Binocrit solution as you have been shown by your doctor. You should check with your doctor or pharmacist if you are not sure.

<u>Pre-filled syringe without needle safety guard</u>



6. Always keeping your skin pinched, depress the plunger slowly and evenly.
7. After injecting the liquid, remove the needle and let go of your skin. Apply pressure over the injection site with a dry, sterile pad.
8. Discard any unused product or waste material. Only use each syringe for one injection.

<u>Pre-filled syringe with needle safety guard</u>



6. Always keeping your skin pinched, depress the plunger slowly and evenly until the entire dose has been given and the plunger cannot be depressed any further. Do not release the pressure on the plunger!
7. After injecting the liquid, remove the needle while maintaining pressure on the plunger and then let go of your skin. Apply pressure over the injection site with a dry, sterile pad.
8. Let go of the plunger. The needle safety guard will rapidly move to cover the needle.
9. Discard any unused product or waste material. Only use each syringe for one injection.

7. MARKETING AUTHORISATION HOLDER

Sandoz Products Malaysia Sdn. Bhd.
Unit 1202, Level 12, Uptown 1,
No. 1, Jalan SS 21/58
Damansara Uptown,
47400 Petaling Jaya,
Selangor.

8. DATE OF REVISION OF THE TEXT

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