PRESCRIBING INFORMATION

Binocrit is a biosimilar medicinal product.

1. NAME OF THE MEDICINAL PRODUCT

Binocrit 1,000 IU/0.5 ml solution for injection in a pre-filled syringe

Binocrit 2,000 IU/1 ml solution for injection in a pre-filled syringe

Binocrit 3,000 IU/0.3 ml solution for injection in a pre-filled syringe

Binocrit 4,000 IU/0.4 ml solution for injection in a pre-filled syringe

Binocrit 5,000 IU/0.5 ml solution for injection in a pre-filled syringe

Binocrit 6,000 IU/0.6 ml solution for injection in a pre-filled syringe

Binocrit 8,000 IU/0.8 ml solution for injection in a pre-filled syringe

Binocrit 10,000 IU/1 ml solution for injection in a pre-filled syringe

Binocrit 20,000 IU/0.5 ml solution for injection in a pre-filled syringe

Binocrit 30,000 IU/0.75 ml solution for injection in a pre-filled syringe

Binocrit 40,000 IU/1 ml solution for injection in a pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Binocrit 1,000 IU/0.5 ml:
Each ml of solution contains 2,000 IU of epoetin alfa* corresponding to 16.8 micrograms per ml
1 pre-filled syringe of 0.5 ml contains 1,000 international units (IU) corresponding to 8.4 micrograms epoetin alfa
Binocrit 2,000 IU/1 ml:
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
Binocrit 3,000 IU/0.3 ml:
Each ml of solution contains 10,000 IU of epoetin alfa* corresponding to 84.0 micrograms per ml
1 pre-filled syringe of 0.3 ml contains 3,000 international units (IU) corresponding to 25.2 micrograms epoetin alfa
Binocrit 4,000 IU/0.4 ml:
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
Binocrit 5,000 IU/0.5 ml:
Each ml of solution contains 10,000 IU of epoetin alfa* corresponding to 84.0 micrograms per ml
1 pre-filled syringe of 0.5 ml contains 5,000 international units (IU) corresponding to 42.0 micrograms epoetin alfa
Binocrit 6,000 IU/0.6 ml:
Each ml of solution contains 10,000 IU of epoetin alfa* corresponding to 84.0 micrograms per ml
1 pre-filled syringe of 0.6 ml contains 6,000 international units (IU) corresponding to 50.4 micrograms epoetin alfa
Binocrit 8,000 IU/0.8 ml:
Each ml of solution contains 10,000 IU of epoetin alfa* corresponding to 84.0 micrograms per ml
1 pre-filled syringe of 0.8 ml contains 8,000 international units (IU) corresponding to 67.2 micrograms epoetin alfa
Binocrit 10,000 IU/1 ml:
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
Binocrit 20,000 IU/0.5 ml:
Each ml of solution contains 40,000 IU of epoetin alfa* corresponding to 336.0 micrograms per ml
1 pre-filled syringe of 0.5 ml contains 20,000 international units (IU) corresponding to 168.0 micrograms epoetin alfa
Binocrit 30,000 IU/0.75 ml:
Each ml of solution contains 40,000 IU of epoetin alfa* corresponding to 336.0 micrograms per ml
1 pre-filled syringe of 0.75 ml contains 30,000 international units (IU) corresponding to 252.0 micrograms epoetin alfa
Binocrit 40,000 IU/1 ml:
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 Chinese Hamster Ovary (CHO) cells by recombinant DNA technology
For a full list of excipients, see section 6.1 "list of excipients".
The medicinal product contains less than 1 mmol sodium (23mg) per dose, i.e. essentially "sodium free".

3. PHARMACEUTICAL FORM

Solution for injection in a pre-filled syringe (injection)
Clear colorless solution.
Binocrit is a biosimilar medicinal product that has been demonstrated to be similar in quality, safety and efficacy to the reference medicinal product Eprex. Please be aware of any differences in the indications between the biosimilar medicinal product and the reference medicinal product. The biosimilar is not to be switched with the reference medicinal product unless specifically stated otherwise. More detailed information regarding biosimilar medicinal products is available on the website of the Ministry of Health:
https://www.health.gov.il/UnitsOffice/HD/MTI/Drugs/Registration/Pages/Biosimilars.aspx

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Binocrit is indicated for the treatment of symptomatic anemia associated with chronic renal failure (CRF):
- in adults and children aged 1 to 18 years on haemodialysis and adult patients on peritoneal dialysis (see section 4.4).
- in adults with renal insufficiency not yet undergoing dialysis for the treatment of severe anemia of renal origin accompanied by clinical symptoms in patients (see section 4.4).

Binocrit is indicated in adult patients 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 anemia at the start of chemotherapy) for the treatment of anaemia and reduction of transfusion requirements.

Binocrit is indicated in adults in a predonation programme to increase the yield of autologous blood. Treatment should only be given to patients with moderate anemia (haemoglobin (Hb) concentration range between 10-13 g/dl (6.2-8.1 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).

Binocrit is indicated for non-iron deficient adult 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 anemia (e.g. Hb concentration range between 10-13 g/dl or 6.2-8.1 mmol/l) who do not have an autologous predonation programme available and with an expected blood loss (900 to 1800 ml).

4.2 Posology and method of administration

Treatment with Binocrit has to be initiated under the supervision of physicians experienced in the management of patients with the above indications.

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 anemia in adult chronic renal failure patients:

Anemia 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). Binocrit should be administered in order to increase haemoglobin to not greater than 12 g/dl (7.5 mmol/l). A rise in haemoglobin of greater than 2 g/dl (1.25 mmol/l) over a four week period should be avoided. If it occurs, appropriate dose adjustment should be made as provided.

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

A sustained haemoglobin level of greater than 12 g/dl (7.5 mmol/l) should be avoided. If the haemoglobin is rising by more than 2 g/dl (1.25 mmol/l) per month, or if the sustained haemoglobin exceeds 12 g/dl (7.5 mmol/l) reduce the Binocrit 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 Binocrit therapy at a dose 25% below the previous level.

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

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

Treatment with Binocrit 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 10g/dl to12 g/dl (6.2-7.5 mmol/l).

Patients with very low initial haemoglobin (< 6 g/dl or < 3.75 mmol/l) may require higher maintenance doses than those whose initial anemia is less severe (Hb > 8 g/dl or > 5 mmol/l).

Adult patients with renal insufficiency not yet undergoing dialysis

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

Correction phase:

Starting dose of 50 IU/kg 2 times a 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 anemia:

Anemia 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.

Binocrit 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, Binocrit 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).

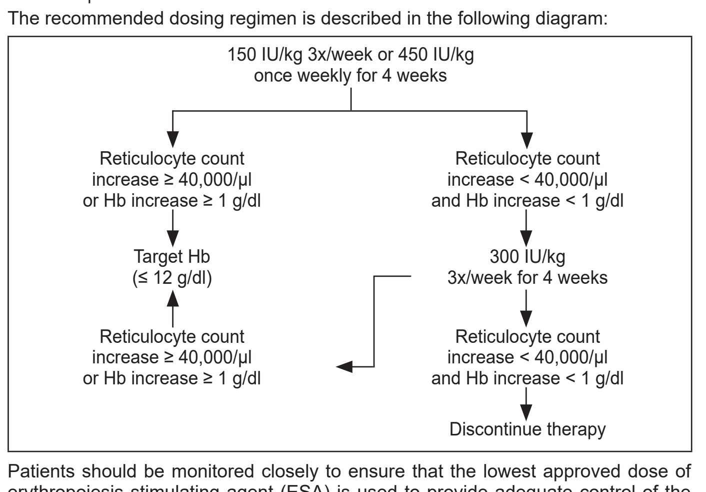
Due to intra-patient variability, occasional individual haemoglobin values for a patient above and below the desired haemoglobin level may be observed. Haemoglobin variability should be addressed through dose management with consideration for the haemoglobin target range of 10 g/dl (6.2 mmol/l) to 12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

- If haemoglobin has increased by at least 1 g/dl (> 0.62 mmol/l) or the reticulocyte count has increased ≥ 40,000 cells/µl above baseline after 4 weeks of treatment, the dose should remain at 150 IU/kg 3 times a week or 450 IU/kg once weekly.
  If the haemoglobin increase is < 1 g/dl (< 0.62 mmol/l) and the reticulocyte count has increased < 40,000 cells/µl 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 has increased ≥ 1 g/dl (≥ 0.62 mmol/l) or the reticulocyte count has increased ≥ 40,000 cells/µl the dose should remain at 300 IU/kg 3 times per week.
- if the haemoglobin has increased < 1 g/dl (< 0.62 mmol/l) and the reticulocyte count has increased < 40,000 cells/µl above baseline, response is unlikely and treatment should be discontinued.

Dosage adjustment to maintain haemoglobin concentration between 10 g/dl-12 g/dl (6.2-7.5 mmol/l):

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

Epoetin alfa 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 33-39%) requiring predeposit of ≥4 units of blood should be treated with Binocrit at a dose of 600 IU/kg intravenously, 2 times weekly for 3 weeks prior to surgery. Binocrit 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 Binocrit 600 IU/kg, administered subcoutanously weekly for three weeks (days 21, 14 and 7) prior to surgery and on the day of surgery (day 0). In cases where there is a medical need to shorten the lead time before surgery to less than three weeks, Binocrit 300 IU/kg epoetin alfa should be administered subcoutanously 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 (9.38 mmol/l), or higher, during the perioprative period, administration of Binocrit should be stopped and further dosages should not be administered.

Paediatric population:

Treatment of symptomatic anemia in chronic renal failure patients on haemodialysis

Anemia 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). Binocrit 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 Binocrit is used to provide adequate control of anaemia and of the symptoms of anemia.

Treatment with Binocrit 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 epoetin alfa in chronic renal failure patients with anemia before initiation of dialysis or on peritoneal dialysis have not been established. Currently available data for subcutaneous use of epoetin alfa 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 epoetin alfa 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 epoetin alfa 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 epoetin alfa 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 Binocrit syringe to stand until it reaches room temperature. This usually takes between 15 and 30 minutes.
As with any other injectable product, check that there are no particles in the solution or change in colour. Binocrit is a sterile but unpreserved product and is for single use only. Administer the amount required.

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 Binocrit 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 as a subcutaneous injection.

Treatment of adult patients with chemotherapy-induced anaemia

Binocrit should be administered as a subcutaneous injection.

Treatment of adult surgery patients in an autologous predonation programme

Binocrit should be administered by the intravenous route.

Treatment of adult patients scheduled for major elective orthopaedic surgery

Binocrit 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 Binocrit 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 injection is preferable in patients who react to the treatment with "flu-like" symptoms. (see section 4.8).
Do not administer Binocrit by intravenous infusion or in conjunction with other medicinal product solutions (please refer to section 6.6 for further information).

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 are given in the limbs or the anterior abdominal wall.
In those situations in which the physician determines that a patient or caregiver can safely and effectively administer Binocrit subcutaneously, instruction as to the proper dosage and administration should be provided.

Graduation rings

The syringe contains graduation rings 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 Binocrit from each syringe should be taken.
"Instructions on how to inject Binocrit yourself" can be found at the end of the package leaflet.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1: "List of 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: "special warnings and precautions for use").
- Uncontrolled hypertension.
- All contraindications associated with autologous blood predonation programme 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 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

General

In all patients receiving Binocrit, blood pressure should be closely monitored and controlled as necessary. Binocrit should be used with caution in the presence of untreated, inadequately treated or poorly controllable hypertension. It may be necessary to add or increase antihypertensive treatment. If blood pressure cannot be controlled, Binocrit 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: "Undesirable effects").

Epoetin alfa should also be used with caution in patients with epilepsy, history of seizures, or medical condition 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 with hepatic dysfunction.

An increased incidence of thrombotic vascular events (TVEs) has been observed in patients receiving ESAs (see section 4.8). These include venous and arterial thromboses and embolism (including some with fatal outcomes), such as deep venous thrombosis, pulmonary emboli, retinal thrombosis, and myocardial infarction. Additionally, cerebrovascular accidents (including cerebral infarction, cerebral haemorrhage and transient ischaemic attacks) have been reported.

The reported risk of these TVEs should be carefully weighed against the benefits to be derived from treatment with epoetin alfa particularly in patients with pre-existing risk factors for TVE, including obesity and prior history of TVEs (e.g. deep venous thrombosis, pulmonary embolism, and cerebral vascular accident).

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

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

All other causes of anaemia (iron, folate or vitamin B_{12} deficiency, aluminium intoxication, infection or inflammation, blood loss, haemolysis and bone marrow fibrosis of any origin) should be evaluated and treated prior to initiating therapy with epoetin alfa, and when deciding to increase the dose. In most cases, the ferritin values in the serum fall simultaneously with the rise in packed cell volume. In order to ensure optimum response to epoetin alfa, adequate iron stores should be assured and iron supplementation should be administered if necessary (see section 4.2). For the selection of the best treatment option according to the patient's needs, current treatment guidelines on iron supplementation in combination with dose instructions approved and outlined in the SmPC of the iron medication should be followed:
- For chronic renal failure patients, iron supplementation is recommended if serum ferritin levels are below 100 ng/mL.
- For cancer patients, iron supplementation is recommended if transferrin saturation is below 20%.
- For patients in an autologous predonation programme, iron supplementation should be administered several weeks prior to initiating the autologous predeposit in order to achieve high iron stores prior to starting epoetin alfa therapy, and throughout the course of epoetin alfa therapy.
- For patients scheduled for major elective orthopaedic surgery, iron supplementation should be administered throughout the course of epoetin alfa therapy. If possible, iron supplementation should be initiated prior to starting epoetin alfa therapy to achieve adequate iron stores.

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

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

At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, Binocrit 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 Binocrit, treatment with Binocrit must not be restarted in this patient at any time.

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

Antibody-mediated 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 is not approved in the management of anemia associated with hepatitis C.

In patients developing sudden lack of efficacy defined by a decrease in haemoglobin (1 to 2 g/dl or 0.62 to 1.25 mmol/l 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 and haemolysis) should be investigated.

A paradoxical decrease in haemoglobin and development of severe anemia 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 anemia in adult and paediatric chronic renal failure patients

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

In chronic renal failure patients the rate of increase in haemoglobin should be approximately 1 g/dl (0.62 mmol/l) per month and should not exceed 2 g/dl (1.25 mmol/l) per month to minimize 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: "Posology and method of administration". In clinical studies, an increased risk of death, 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 studies have not shown significant benefits attributable to the administration of epoetins when haemoglobin concentration is increased beyond the level necessary to control symptoms of anemia and to avoid blood transfusion.

Caution should be exercised with escalation of Binocrit 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: "Posology and method of administration" and 5.1: "Pharmacodynamic properties").

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: "Pharmacodynamic properties") and may require an increase in epoetin alfa dose. Haemoglobin levels should be monitored regularly.

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

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

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

Based on information available to date, correction of anemia 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 anemia

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 (RBC) 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 tumor control or decreased overall survival:
- decreased locoregional control in patients with advanced head and neck cancer receiving radiation therapy when administered to target a haemoglobin 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 target a haemoglobin of 12-14 g/dl (7.5-8.7 mmol/l),
- increased risk of death when administered to target a haemoglobin 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 progress of disease (PD) or death in the epoetin alfa plus standard of care 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 anemia in patients with cancer. The decision to administer recombinant erythropoietins should be based on a benefit-risk assessment with the participation of the individual patient, which should also 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 anemia; life-expectancy; the environment in which the patient is being treated; and patient preference (see section 5.1: "Pharmacodynamic properties").

In cancer patients receiving chemotherapy, the 2 to 3 weeks 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 programme

All special warnings and 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 deep vein thrombosis (DVTs). Moreover, in patients with a baseline haemoglobin 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, epoetin alfa should not be used in patients with baseline haemoglobin > 13 g/dl (>8.1 mmol/l).

Excipients:

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, 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.

Medicinal products that decrease erythropoiesis may decrease the response to epoetin alfa.

Since cyclosporin is bound by red blood cells (RBCs) there is potential for medicinal product 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 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 or limited amount of data from the use of epoetin alfa in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3: "Preclinical safety data").
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 programme.

Breast feeding

It is not known whether epoetin alfa is excreted in human milk. A risk to the newborns/infants cannot be excluded.
Epoetin alfa should be used with caution in nursing women. A decision must be made whether to discontinue breast feeding or to discontinue/abstain from therapy with epoetin alfa 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.
Binocrit has no or negligible influence on the ability to drive and use machines.

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: "Special warnings and precautions for use").

The most frequently occurring adverse drug reactions observed in clinical studies 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: "Special warnings and precautions for use").

Tabulated List of Adverse reactions

Of a total 3,417 subjects in 25 randomised, double-blinded, placebo or standard of care controlled studies, the overall safety profile of epoetin alfa was evaluated in 2,094 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] 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 ≥ 1% of subjects treated with epoetin alfa in these studies are shown in the table below.

Frequencies estimate Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

MedDRA System Organ Classification (SOC)	Adverse Reaction (Preferred Term Level)	Frequency
Blood and lymphatic system disorders	Pure red cell aplasia[3], Thrombocythaemia	Rare
Metabolism and nutrition disorders	Hyperkalaemia[1]	Uncommon
Immune system disorders	Hypersensitivity[3]	Uncommon
	Anaphylactic reaction[3]	Rare
Nervous system disorders	Headache	Common
	Convulsion	Uncommon
Vascular disorders	Hypertension, Venous and arterial thromboses[2]	Common
	Hypertensive crisis[3]	Not known
Respiratory, thoracic and mediastinal disorders	Cough	Common
	Respiratory tract congestion	Uncommon
Gastrointestinal disorders	Diarrhoea, Nausea, Vomiting	Very common
Skin and subcutaneous tissue disorders	Rash	Common
	Urticaria[3]	Uncommon
	Angioneurotic oedema[3]	Not known
Musculoskeletal and connective tissue disorders	Arthralgia, Bone pain, Myalgia, Pain in extremity	Common
Congenital, familial and genetic disorders	Porphyria acute[3]	Rare
General disorders and administration site conditions	Pyrexia	Very common
	Chills, Influenza like illness, Injection site reaction, Oedema peripheral	Common
	Medicinal product ineffective[3]	Not known
Investigations	Anti-erythropoietin 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 (see section 4.4: "Special warnings and precautions for use").
SCARs including SJS and 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: "Special warnings and precautions for use").
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: "Special warnings and precautions for use"). More cases have been reported with subcutaneous (SC) route of administration, compared with the IV route.

Paediatric population with chronic renal failure on haemodialysis

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

Reporting of suspected adverse reactions

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

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 or haematocrit levels occur. Additional supportive care should be provided as necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antianemic preparations other antianemic 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 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 pharmacodynamics 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 anemic 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 anemia

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 anemic 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 anemic 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 anemic 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 in anemic 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 pre-treatment 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 studies in adult anemic CRF patients, including haemodialysis and pre-dialysis patients, to treat anemia and maintain haematocrit within a target concentration range of 30 to 36%.
In clinical studies 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 studies 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, multicenter, 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 studies 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 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 epoetin alfa (3 times per week, once weekly, once every 2 weeks, and once every 4 weeks) some patients with longer dosing intervals did not maintain adequate haemoglobin levels and reached protocol-defined haemoglobin withdrawal criteria (0% in once weekly, 3.7% in once-every-2-weeks, and 3.3% in the once-every-4-weeks groups).
A randomised prospective study evaluated 1,432 anemic chronic renal failure patients who were not undergoing dialysis. Patients were assigned to epoetin alfa treatment targeting a maintenance haemoglobin level of 13.5 g/dl (higher than the recommended haemoglobin concentration level) or 11.3 g/dl. A major cardiovascular event (death, myocardial infarction, stroke or hospitalisation for congestive heart failure) occurred among 125 (18%) of the 715 patients in the higher haemoglobin group compared to 97 (14%) among the 717 patients in the lower haemoglobin group (hazard ratio [HR] 1.3, 95% CI: 1.0, 1.7, p = 0.03).
Pooled post-hoc analyses of clinical studies of ESAs have been performed in chronic renal failure patients (on dialysis, not on dialysis, in diabetic and non-diabetic patients). A tendency towards increased risk estimates for all-cause mortality, cardiovascular and cerebrovascular events associated with higher cumulative ESA doses independent of the diabetes or dialysis status was observed (see section 4.2 and section 4.4).

Treatment of patients with chemotherapy-induced anemia

Epoetin alfa has been studied in clinical studies in adult anemic cancer patients with lymphoid and solid tumors, and patients on various chemotherapy regimens, including platinum and non-platinum-containing regimens. In these studies, 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 anemic 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 studies was demonstrated by a similar area under the neutrophil time curve in patients treated with epoetin alfa and placebo-treated patients, as well as by a similar proportion of patients in groups treated with epoetin alfa and placebo-treated groups whose absolute neutrophil counts fell below 1,000 and 500 cells/µl.
In a prospective, randomised, double-blind, placebo-controlled study conducted in 375 anemic patients with various non-myeloid malignancies receiving non-platinum chemotherapy, there was a significant reduction of anemia -related sequelae (e.g. fatigue, decreased energy, and activity reduction), as measured by the following instruments and scales: Functional Assessment of Cancer Therapy-Anemia (FACT-An) general scale, FACT-An fatigue scale, and Cancer Linear Analogue Scale (CLAS). Two other smaller, randomised, placebo-controlled studies 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: anemia 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 (8.1 mmol/l); in the remaining three studies it was 12 to 14 g/dl (7.5 to 8.7 mmol/l). 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 anemia associated with various common cancers who received recombinant human erythropoietin compared to controls. Overall survival outcome in the studies 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 studies 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 studies 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 studies 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: "Special warnings and precautions for use").
A randomised, open-label, multicentre study was conducted in 2,098 anemic women with metastatic breast cancer, who received first line or second line chemotherapy. This was a non inferiority study designed to rule out a 15% risk increase in tumour progression or death of epoetin alfa plus standard of care as compared with standard of care 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 standard of care arm (5.8% versus 11.4%); however, significantly more patients had thrombotic vascular events in the epoetin alfa plus standard of care arm (2.8% versus 1.4%) At the final analysis, 1653 deaths were reported. Median overall survival in the epoetin alfa plus standard of care group was 17.8 months compared with 18.0 months in the standard of care 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 standard of care group and 7.5 months in the standard of care 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 standard of care group and 8.3 months in the standard of care 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 anemia 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 study 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. 16% 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 study in non-iron deficient adult subjects with a pre-treatment 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 pre-treatment to pre-surgery, the mean increase in haemoglobin in the 600 IU/kg weekly group (1.44 g/dl) was twice than that observed in the 300 IU/kg daily group (0.73 g/dl). Mean haemoglobin levels were similar for the two treatment groups throughout the postsurgical period.
The erythropoietic response observed in both treatment groups resulted in similar transfusion rates (16% in the 600 IU/kg weekly group and 20% in the 300 IU/kg daily group).

Paediatric population

Chronic renal failure

Epoetin alfa was evaluated in an open-label, non-randomised, open dose-range, 52-week clinical study in paediatric CRF patients undergoing haemodialysis. The median age of patients enrolled in the study was 11.6 years (range 0.5 to 20.1 years).
Epoetin alfa was administered at 75 IU/kg/week intravenously in 2 or 3 divided doses post-dialysis, titrated by 75 IU/kg/week at intervals of 4 weeks (up to a maximum of 300 IU/kg/week), to achieve a 1 g/dl/month increase in haemoglobin. The desired haemoglobin concentration range was 9.6 to 11.2 g/dl. 81% 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 21 associated with positive trends towards higher haemoglobin levels. No unexpected adverse reactions were reported (see section 4.2).

Chemotherapy-induced anemia

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 anemic 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 anemic cancer subjects were 45.8 and 11.3 ml/h/kg, respectively. In most anemic 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 bi-weekly), 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 toxicological studies in dogs and rats, but not in monkeys, epoetin alfa therapy was associated with subclinical bone marrow fibrosis (bone marrow fibrosis is a known complication of chronic renal failure in humans and may be related to secondary hyperparathyroidism or unknown factors. The incidence of bone marrow fibrosis was not increased in a study of haemodialysis patients who were treated with epoetin alfa for 3 years compared to a matched control group of dialysis patients who had not been treated with epoetin alfa.
Epoetin alfa does not induce bacterial gene mutation (Ames test), chromosomal aberrations in mammalian cells, micronuclei in mice, or gene mutation at the HGPRT locus.
Long-term carcinogenicity studies have not been carried out. Conflicting reports in the literature, based on in vitro findings from human tumour samples, suggest erythropoietins may play a role as tumour proliferators. This is of uncertain significance in the clinical situation.
In cell cultures of human bone marrow cells, epoetin alfa stimulates erythropoiesis specifically and does not affect leucopoiesis. Cytotoxic actions of epoetin alfa on bone marrow cells could not be detected.
In animal studies, epoetin alfa has been shown to decrease foetal body weight, delay ossification and increase foetal mortality when given in weekly doses of approximately 20 times the recommended human weekly dose. These changes are interpreted as being secondary to decreased maternal body weight gain and the significance to humans is unknown given therapeutic dose levels.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

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

6.3 Shelf-life

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

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.
Do not freeze or shake.
Store in the original package in order to protect from light.
For the purpose of ambulatory use, the patient may remove Binocrit from the refrigerator and store it not above 25°C for one single period of up to 3 days. If the medicinal product has not been used at the end of this period, it should be disposed of.

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

7. LICENSE HOLDER AND IMPORTER'S NAME AND ADDRESS

Sandoz Pharmaceuticals Israel Ltd., P.O.Box 9015, Tel Aviv

Registration number:
147-08-33360-00/ 147-09-33361-00/ 147-17-33370-00/ 147-11-33363-00/ 147-12-33364-00/ 147-13-33365-00/ 147-14-33366-00/ 147-15-33367-00/ 147-16-33368-00/ 147-10-33362-00/ 147-18-33372-00

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