NEW ZEALAND DATA SHEET
BINOCRIT (EPOETIN ALFA (RCH)) SOLUTION FOR INJECTION

Use in Cancer

In some studies, use of Erythropoiesis Stimulating Agents (ESAs) to treat anaemia in patients with cancer has been associated with increased mortality. ESAs should only be used to treat anaemia that has developed as a result of concomitantly administered chemotherapy, and only when blood transfusion is not considered appropriate. Haemoglobin levels should not exceed 120 g/L (see Section 4.4 Special warnings and precautions for use).

1 PRODUCT NAME

Binocrit 1,000 IU/0.5 mL solution for injection in pre-filled syringe.

Binocrit 2,000 IU/1.0 mL solution for injection in pre-filled syringe.

Binocrit 3,000 IU/0.3 mL solution for injection in pre-filled syringe.

Binocrit 4,000 IU/0.4 mL solution for injection in pre-filled syringe.

Binocrit 5,000 IU/0.5 mL solution for injection in pre-filled syringe.

Binocrit 6,000 IU/0.6 mL solution for injection in pre-filled syringe.

Binocrit 7,000 IU/0.7 mL solution for injection in pre-filled syringe.

Binocrit 8,000 IU/0.8 mL solution for injection in pre-filled syringe.

Binocrit 9,000 IU/0.9 mL solution for injection in pre-filled syringe.

Binocrit 10,000 IU/1.0 mL solution for injection in pre-filled syringe.

Binocrit 20,000 IU/0.5 mL solution for injection in pre-filled syringe.

Binocrit 30,000 IU/0.75 mL solution for injection in pre-filled syringe.

Binocrit 40,000 IU/1.0 mL solution for injection in pre-filled syringe.

Binocrit is a biosimilar medicine.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Binocrit is a sterile, clear and colourless, preservative-free buffered protein solution of epoetin alfa (rch).

Table 1. Binocrit dose strengths and the corresponding quantity of epoetin alpha per mL

Binocrit dose strength	Filled volume	Total content of active	Concentration
1000 IU	0.5 mL	8.4 microgram	16.8 microgram/mL
2000 IU	1.0 mL	16.8 microgram	16.8 microgram/mL
3000 IU	0.3 mL	25.2 microgram	84.0 microgram/mL
4000 IU	0.4 mL	33.6 microgram	84.0 microgram/mL
5000 IU	0.5 mL	42.0 microgram	84.0 microgram/mL
6000 IU	0.6 mL	50.4 microgram	84.0 microgram/mL

7000 IU	0.7 mL	58.8 microgram	84.0 microgram/mL
8000 IU	0.8 mL	67.2 microgram	84.0 microgram/mL
9000 IU	0.9 mL	75.6 microgram	84.0 microgram/mL
10,000 IU	1.0 mL	84.0 microgram	84.0 microgram/mL
20,000 IU	0.5 mL	168.0 microgram	336.0 microgram/mL
30,000 IU	0.75 mL	252.0 microgram	336.0 microgram/mL
40,000 IU	1.0 mL	336.0 microgram	336.0 microgram/mL

For the full list of excipients, see Section 6.1 List of excipients.

Binocrit is a biosimilar medicine. Prior to dispensing Binocrit the prescribing physician should review the bioequivalence data (see Section 5 Pharmacological Properties) to determine whether Binocrit is interchangeable with the reference medicine epoetin alfa (rch) marketed in New Zealand. Erythropoiesis-stimulating agents (ESAs) are not necessarily equivalent. Therefore, it should be emphasised that patients should only be switched from one ESA (such as epoetin alfa) to another ESA with the authorisation of the treating physician. For further information refer to http://www.medsafe.govt.nz/profs/RIss/Biosimilars.asp.

3 PHARMACEUTICAL FORM

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

Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Binocrit is indicated for:

- the treatment of severe anaemia of renal origin accompanied by clinical symptoms in patients with renal insufficiency not yet undergoing dialysis
- anaemia associated with chronic renal failure in paediatric and adult patients on dialysis
- anaemia in patients with non-myeloid malignancies where anaemia is due to the effect of concomitantly administered chemotherapy, and where blood transfusion is not considered appropriate.
- adult patients with mild-to-moderate anaemia (haemoglobin > 100 to < 130 g/L) scheduled for elective surgery with an expected moderate blood loss (2-4 units or 900 to 1800 mL) to reduce exposure to allogeneic blood transfusion and to facilitate erythropoietic recovery
- to augment autologous blood collection and to limit the decline in haemoglobin in anaemic adult patients undergoing major surgery who are not expected to pre-deposit their complete peri-operative blood needs.

4.2 DOSE AND METHOD OF ADMINISTRATION

During therapy, haematological parameters should be monitored regularly. Doses must be individualised to ensure that haemoglobin is maintained at an appropriate level for each patient.

As a single anaphylactic reaction was observed in one patient during the course of clinical testing, it is recommended that the first dose be administered under medical supervision.

Method of Administration

- Parenteral medicine products should be visually inspected for particulate matter and discolouration prior to administration. Product exhibiting particulate matter or discolouration must not be used. Do not shake, as shaking may denature the glycoprotein, rendering it inactive.
- Binocrit in single use syringes contains no preservatives. Do not re-use syringe. Discard unused portion.
- Prepare Binocrit for injection from the prefilled syringe.
- Administer as i.v. or s.c. injection over 1-2 minutes. In patients on dialysis the injection should follow the dialysis procedure. Slow injection over 5 minutes may be beneficial to those who experience flu-like symptoms. For subcutaneous dosing a maximum volume of 1 mL at any one injection site should not be exceeded. In the case of larger volumes, the injection should be divided between more than one site.
- Do not dilute or transfer to any other container. Do not administer by intravenous infusion or in conjunction with other medicine solutions.

The pre-filled syringes are fitted with or without a needle safety guard. The needle safety guard device helps prevent needle stick injuries after use. The Binocrit Consumer Medicine Information includes full instructions for the use and handling of pre-filled syringes.

For treatment of anaemia associated with renal insufficiency or chronic renal failure

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 (patient not yet on dialysis and peritoneal dialysis patients) Binocrit may be administered subcutaneously (See Section 4.4 Special warnings and precautions for use – Pure Red Cell Aplasia).

In patients maintained on haemodialysis, Binocrit should always be administered after completion of dialysis.

Adults

The recommended starting dose of epoetin alfa (rch) is 50 IU/kg, three times per week, administered as i.v. or s.c injection over 1-2 minutes. Further dose increments should depend upon the initial response (proposed rate < 20 g/L per month). Because of the length of time required for erythropoiesis - several days for erythroid progenitors to mature and be released into the circulation - a clinically significant increase in haematocrit is usually not observed in less than 2 weeks and may require up to 6 weeks in some patients.

If required, dose increments in steps of 25 IU/kg in intervals of four weeks are recommended. If the rate of haemoglobin (Hb) rise exceeds 20 g/L per month at 50 IU/kg, three times per week, downward dosage adjustments should be made in the amount administered in each dose and by omitting one of the weekly doses. Similar downward dose adjustments should be made if the Hb level exceeds 120 g/L. Maximum dose should generally not exceed 200 IU/kg three times per week.

When a target haemoglobin concentration of 100-120 g/L (95 to 110 g/L in paediatric patients) has been achieved, the total maintenance weekly dose (average 100-300 IU/kg) can be

apportioned in two or three injections. Caution should be exercised with escalation of epoetin alfa doses in patients with chronic renal failure.

In patients with chronic renal failure, maintenance haemoglobin concentration should not exceed the upper limit of the haemoglobin concentration range.

Available data indicate that patients starting treatment at very low Hb levels (< 60 g/L) may require higher maintenance dosages than those starting therapy with Hb above 80 g/L; the latter group of patients may need weekly doses as low as 100 IU/kg.

Children

For paediatric haemodialysis patients:

The treatment is divided into 2 stages:

Correction phase

50 IU/kg/3 times per week by the intravenous or subcutaneous route. When a dose adjustment is necessary, this should be done in steps of 25 IU/kg/3 times per week at intervals of at least 4 weeks until the desired goal is achieved.

Maintenance phase

Appropriate adjustment of the dose should be made in order to maintain the haemoglobin concentration within the desired range between 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.

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

The clinical data available suggest that those patients whose initial haemoglobin is very low (< 6.8 g/dL) may require higher maintenance doses than those whose initial anaemia is less severe (> 6.8 g/dL).

For treatment of anaemia associated with non-myeloid malignancies

Adults

The haemoglobin concentration range should be between 100 to 120 g/L in men and women, and it should not be exceeded.

Starting dose

The recommended starting dose of Binocrit is 150 lU/kg as a subcutaneous injection three times per week for 4 weeks.

Increase dose

If the haemoglobin has increased by at least 10 g/L (0.62 mmol/L) or the reticulocyte count has increased ≥ 40,000 cells/microlitre above baseline after 4 weeks of treatment, the dose should remain at 150 IU/kg. If the haemoglobin increase is < 10 g/L (< 0.62 mmol/L) and the

reticulocyte count has increased < 40,000 cells/microlitre above baseline, increase the dose to 300 IU/kg.

If after an additional 4 weeks of therapy at 300 IU/kg, the haemoglobin has increased ≥ 10 g/L (≥ 0.62 mmol/L) or the reticulocyte count has increased ≥ 40,000 cells/microlitre the dose should remain at 300 IU/kg. However, if the haemoglobin has increased < 10 g/L (< 0.62 mmol/L) and the reticulocyte count has increased < 40,000 cells/microlitre above baseline, response is unlikely and treatment should be discontinued.

A rate of rise in haemoglobin of greater than 10 g/L per 2 week or 20 g/L per month, or haemoglobin levels of > 120 g/L should be avoided. If the haemoglobin is rising by more than 10 g/L per two week or 20 g/L per month, or haemoglobin is approaching 120 g/L, reduce the epoetin alfa (rch) dose by about 25-50% depending on the rate of rise of haemoglobin. If the haemoglobin exceeds 120 g/L, withhold therapy until it falls below 120 g/L and then reinitiate epoetin alfa (rch) at a dose 25% below the previous dose.

Patients should be monitored closely to ensure that the lowest approved dose of epoetin alpha (rch) is used to provide adequate control of the symptoms of anaemia.

Adult patients scheduled for elective surgery

The subcutaneous route of administration should be used.

The recommended dose regimen is 600 IU/kg 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 shorten the lead time before surgery to less than three weeks, 300 IU/kg Binocrit should be given daily for 10 consecutive days prior to surgery, on the day of surgery, and for four days immediately thereafter. The administration of Binocrit should be stopped as soon as the haemoglobin level reaches 150 g/L in the pre-operative period, even if not all the planned Binocrit doses have been given.

Anaemic adult surgery patients in an Autologous Pre-donation Programme (ABD)

The intravenous route should be used. The recommended dose is 300 - 600 IU/kg twice weekly for three weeks, together with at least 200 mg oral elemental iron daily.

4.3 CONTRAINDICATIONS

- Binocrit is contraindicated in patients with uncontrolled hypertension, known sensitivity to mammalian cell derived products, and/or hypersensitivity to any component of the product.
- Patients who develop Pure Red Cell Aplasia (PRCA) following treatment with any erythropoietin product should not receive Binocrit or any other erythropoietin.
- The use of Binocrit in patients scheduled for elective surgery (and who are not participating in an autologous blood pre deposit 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 or treatment.
- All contraindications associated with autologous blood predonation programs should be respected in patients being supplemented with Binocrit.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Cardiovascular and Thrombotic Events / Increased Mortality

Cardiovascular and thrombotic events such as myocardial ischaemia and infarction, cerebrovascular haemorrhage and infarction, transient ischaemic attacks, deep venous thrombosis, arterial thrombosis, pulmonary emboli, retinal thrombosis and haemodialysis graft occlusion have been reported in patients receiving erythropoiesis stimulating agents such as epoetin alfa.

An increased incidence of thrombotic vascular events (TVEs) has been observed in patients receiving Erythropoiesis-stimulating agents ESAs (see Section 4.8 Undesirable effects). 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 TVEs should be carefully weighed against the benefits to be derived from treatment with epoetin alfa particularly in patients with pre-existing risk factors.

Epoetin alfa (rch) and other erythropoiesis-stimulating agents increased the risk for death and for serious cardiovascular events in controlled clinical trials when administered to target a haemoglobin of greater than 120 g/L. There was an increased risk of serious arterial and venous thromboembolic events, including myocardial infarction, stroke, congestive heart failure and haemodialysis graft occlusion. A rate of haemoglobin rise of greater than 10 g/L over 2 weeks may also contribute to these risks.

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

Growth Factor Potential / Increased Tumour Progression

Epoetin alfa is a growth factor that primarily stimulates red blood cell production. Like all growth factors there is a theoretical concern that epoetin alfa could act as a growth factor for any tumour type, particularly myeloid malignancies. Erythropoiesis-stimulating agents (ESAs), when administered to target a haemoglobin of greater than 120 g/L, shortened the time to tumour progression in patients with advanced head and neck cancer receiving radiation therapy. ESAs also shortened survival in patients with metastatic breast cancer receiving chemotherapy when administered to a target haemoglobin greater than 120 g/L.

Use in Cancer Patients

Cancer patients on epoetin alfa (rch) should have haemoglobin 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 tumour cells. As with all growth factors, there is a concern that ESAs could stimulate the growth of tumours.

In controlled clinical studies, use of epoetin alfa (rch) and other ESAs have shown:

- decreased locoregional control in patients with advanced head and neck cancer receiving radiation therapy when administered to a haemoglobin target of greater than 140 g/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 haemoglobin target of 120-140 g/L
- Another ESA (darbepoetin alfa) increased risk of death when administered to target a haemoglobin of 120 g/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 tumour and its stage; the degree of anaemia; life-expectancy; the environment in which the patient is being treated; and patient preference.

Use in Chronic Renal Failure Patients

Chronic renal failure patients being treated with epoetin alfa (rch) 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 10 g/L per month and should not exceed 20 g/L per month to minimise risks of an increase in hypertension. Dose should be reduced when haemoglobin approaches 120 g/L.

In patients with chronic renal failure, maintenance haemoglobin concentration should not exceed the upper limit of the target haemoglobin concentration range as recommended under Section 4.2 Dose and method of administration. Haemoglobin levels targeted to 130 g/L or higher may be associated with a higher risk of cardiovascular events or cerebrovascular events, including stroke and death.

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

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 (aspirin), 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 the appropriate treatment of the hyperkalaemia, consideration should be given to ceasing epoetin alfa (rch) administration until the serum potassium level has been corrected.

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

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

Hypertension

Patients with uncontrolled hypertension should not be treated with epoetin alfa (rch); blood pressure should be controlled adequately before initiation of therapy. Blood pressure may rise during treatment of anaemia with epoetin alfa (rch). Hypertensive crisis with encephalopathy and seizures, requiring the immediate attention of a physician and intensive medical care, have also occurred during epoetin alfa (rch) 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).

Special care should be taken to closely monitor and control blood pressure in patients treated with epoetin alfa (rch). During epoetin alfa (rch) therapy, patients should be advised of the importance of compliance with antihypertensive therapy and dietary restrictions. If blood pressure is difficult to control after initiation of appropriate measures, the dose of epoetin alfa (rch) should be reduced or temporarily withheld until haemoglobin begins to decrease (see Section 4.2 Dose and method of administration).

Pure Red Cell Aplasia

In chronic renal failure patients, antibody-mediated pure red cell aplasia (PRCA) (erythroblastopaenia) has been rarely reported after months to years of treatment with erythropoietins. Most cases of PRCA associated with epoetin alfa (rch) occurred in patients receiving subcutaneous (SC) administration. The SC route should only be used when intravenous (IV) access is not readily available. Cases also have been rarely reported in patients with hepatitis C treated with interferon and ribavirin, when ESAs are used concomitantly. ESAs are not approved in the management of anaemia associated with hepatitis C.

In most of these PRCA patients, antibodies to erythropoietins have been reported. In patients developing sudden lack of efficacy typical causes of non-response should be investigated. If no cause is identified, a bone marrow examination should be considered.

If pure red cell aplasia (PRCA) is diagnosed, epoetin alfa (rch) must be immediately discontinued and testing for erythropoietin antibodies should be considered. If antibodies to erythropoietin are detected, patients should not be switched to another ESA product as anti-erythropoietin antibodies cross-react with other ESAs. Other causes of pure red cell aplasia should be excluded, and appropriate therapy instituted.

Seizures

Epoetin alfa (rch) 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.

lron Supplementation

Other causes of anaemia (iron, folate or Vitamin B12 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 (rch), 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 (rch), adequate iron stores should be assured and iron supplementation should be administered if necessary:

- For chronic renal failure patients, iron supplementation (elemental iron 200-300 mg/day orally for adults and 100-200 mg/day orally for paediatrics) is recommended if serum ferritin levels are below 100 ng/mL.
- For cancer patients, iron supplementation (elemental iron 200-300 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 (rch) 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 (rch) therapy. If possible, iron supplementation should be initiated prior to starting epoetin alfa (rch) therapy to achieve adequate iron stores.

General

Epoetin alfa (rch) should be used with caution in those patients with pre-existing hypertension, ischaemic vascular disease, epilepsy, history of seizures, or medical conditions associated with a predisposition to seizure activity such as CNS infections and brain metastases.

The safety and effectiveness of epoetin alfa has not been established in patients with underlying haematologic diseases (e.g. haemolytic anaemia, sickle cell disease, thalassemia, porphyria).

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

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

Very rarely, exacerbation of porphyria has been observed in epoetin alfa (rch) treated patients with chronic renal failure. Epoetin alfa (rch) has not caused increased urinary excretion of porphyrin metabolites in normal volunteers, even in the presence of a rapid erythropoietic response.

Nevertheless, epoetin alfa (rch) should be used with caution in patients with known porphyria.

Increased serum uric acid may occur in patients whose haemoglobin is rising more than approximately 20 g/L per month. Consequently epoetin alfa (rch) should be used with caution in patients with a history of gout.

Epoetin alfa (rch) should also be used with caution in patients with chronic liver failure. The safety and dosage regime of epoetin alfa (rch) has not been established in the presence of hepatic dysfunction. Due to decreased metabolism, patients with hepatic dysfunction may have increased erythropoiesis with epoetin alfa (rch).

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 alpha (rch). Discontinue epoetin alpha (rch) therapy immediately if a severe cutaneous reaction, such as SJS/TEN, is suspected.

Renal dialysis

Correction of anaemia with epoetin alfa (rch) does not appear to affect dialysis efficiency. However, an increase in appetite could lead to increased potassium intake and hyperkalaemia in both dialysis and pre-dialysis patients. This and other alterations in serum chemistry should be managed by dietary alterations and modifications of the dialysis prescription, if appropriate.

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 treatment until hyperkalaemia has been corrected.

In some pre-clinical toxicological studies in dogs and rats, but not in monkeys, epoetin alfa (rch) 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 dialysis patients who were treated with epoetin alfa (rch) for 12-19 months compared with the incidence of bone marrow fibrosis in a matched control group of dialysis patients who had not been treated with epoetin alfa (rch). In a 13-week study, dogs were treated subcutaneously or intravenously with 80, 240 or 520 IU/kg/day. The majority of dogs treated subcutaneously and 50% of dogs treated intravenously developed anaemia with or without bone marrow hypoplasia. The cause of these observations is unknown, however, no cases of paradoxical anaemia have been reported in haematologically normal humans treated with epoetin alfa (rch), making the significance of the findings in dogs unclear.

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

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

Use in Patients Scheduled for Elective Surgery

Potentially correctable anaemia should be investigated and appropriately treated before considering therapy with epoetin alfa (rch) prior to elective surgery.

In patients with a baseline haemoglobin of > 130 g/L (8.1 mmol/L), the possibility that epoetin alfa (rch) 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 a baseline haemoglobin > 130 g/L (8.1 mmol/L).

Use in Surgery Patients in an Autologous Pre-Donation Programme (ABD)

All special precautions associated with autologous pre-donation programmes, especially routine volume replacement, should be respected.

Good blood management practices should always be used in the perisurgical setting.

Paediatric Use

Efficacy: Clinical trials of epoetin alfa in children supported the following effects - correction of anaemia; reduction or elimination of transfusion-requirements; improvement of the bleeding tendency in uraemia; increased weight and appetite; and the reduction of cytotoxic antibodies. Possible but not conclusive effects were an improvement in exercise capacity and short-term cardiovascular effects. Long-term cardiovascular effects, effects on growth rate, improved prospects for renal transplantation and improved quality of life were unproved.

Safety: Incomplete information is available, particularly on the rate of change of haemoglobin and blood pressure.

Dose: Available data supports a dose of 25 IU/kg/3 times a week rather than 50 IU/kg/3 times a week.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

There are no known clinically significant medicine interactions, but the effect of epoetin alfa (rch) may be potentiated by the simultaneous therapeutic administration of a haematinic agent such as ferrous sulphate when a deficiency state exists.

Drugs that decrease erythropoiesis may decrease the response to epoetin alfa (rch).

No evidence exists that indicates that treatment with epoetin alfa (rch) alters the metabolism of other drugs. However, since ciclosporin is bound by RBC's there is potential for a drug interaction. If epoetin alfa (rch) is given concomitantly with ciclosporin, blood levels of ciclosporin should be monitored and the dose of ciclosporin adjusted as the haematocrit rises.

No evidence exists that indicates an interaction between epoetin alfa (rch) and G-CSF or GM-CSF with regard to haematological differentiation or proliferation of tumour biopsy specimens *in vitro*.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Use in Pregnancy

The drug is classed as Category B3. Epoetin alfa (rch) should be administered during pregnancy only if clearly needed and if the potential benefit justifies the potential risk to the foetus. It is not known whether epoetin alfa (rch) crosses the placenta or whether it can cause foetal harm when administered to a pregnant woman. Animal studies have shown no evidence of teratogenic activity in rats or rabbits at epoetin alfa (rch) dosages up to 55 IU/kg/day administered intravenously. However, intravenous administration of epoetin alfa (rch) at dose levels of 20-500 IU/kg/day in rats causes decreased fertility, increased pre- and post-implantation loss, decreased foetal weight and retardation of ossification.

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

Use in lactation

Epoetin alfa (rch) should be administered during lactation only if clearly needed. It is not known whether epoetin alfa (rch) is excreted in breast milk or whether it can cause harm to the

infant when administered to a lactating woman. Intravenous administration of the drug to lactating rats at 500 IU/kg/day causes retardation of growth and development of the offspring.

In lactating surgical patients participating in an autologous blood predonation programme, the use of epoetin lambda (rch) is not recommended.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Due to the increased risk of hypertension during the initial phase of epoetin alfa (rch) treatment, patients with chronic renal failure should use caution when performing potentially hazardous activities, such as driving or operating machinery, until the optimal maintenance dose of epoetin alfa (rch) has been established.

4.8 UNDESIRABLE EFFECTS

The most frequent adverse drug effects during treatment with epoetin alfa (rch) 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. The most frequently occurring adverse drug effects 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.

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).

Hypersensitivity reactions, including cases of rash (including urticaria, anaphylactic reaction and angio-oedema 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.

Clinical Trial Experience

Of a total 3559 subjects in 27 randomised, double-blinded, placebo or standard of care controlled studies, the overall safety profile of epoetin alfa (rch) was evaluated in 2136 anaemic subjects. Included were 228 epoetin alfa-treated CRF subjects in 4 chronic renal failure studies (2 studies in predialysis [N = 131 exposed CRF subjects not yet on dialysis] and 2 in dialysis [N = 97 exposed CRF subjects on dialysis]; 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 for autologous blood donation; and 213 exposed subjects in 1 study in the perisurgical setting. Adverse drug effects reported by ≥ 1% of subjects treated with epoetin alfa (rch) in these trials are shown in Tables 2 - 3.

Table 2. Summary of Adverse Drug Effects Reported by ≥ 1% of Subjects in Clinical Registration Trials with epoetin alfa (rch): Chronic Renal Failure

System/Organ Class Adverse Drug Effect	Chronic Renal Failure			
	Predialysis		Dialysis	
	EPO N = 131 n (%)	Placebo N = 79 n (%)	EPO N = 97 n (%)	Placebo N = 46 n (%)
Gastrointestinal disorders				
Nausea	14 (11)	10 (13)	23 (24)	13 (28)
Diarrhoea	16 (12)	8 (10)	7 (7)	4 (9)

System/Organ Class Adverse Drug Effect	Chronic Renal Failure			
	Predialysis		Dialysis	
	EPO N = 131 n (%)	Placebo N = 79 n (%)	EPO N = 97 n (%)	Placebo N = 46 n (%)
Vomiting	12 (9)	6 (8)	9 (9)	8 (17)
General disorders and administration site conditions				
Chills	6 (5)	2 (3)	10 (10)	3 (7)
Influenza like illness	1 (1)	NR	9 (9)	6 (13)
Injection site reaction	14 (11)	16 (20)	1 (1)	NR
Pyrexia	4 (3)	4 (5)	9 (9)	6 (13)
Peripheral oedema	9 (7)	10 (3)	NR	NR
Metabolism and nutrition disorders				
Hyperkalaemia	3 (2)	3 (4)	10 (10)	2 (4)
Musculoskeletal and connective tissue disorders				
Arthralgia	16 (12)	6 (8)	23 (24)	3 (7)
Bone pain	1 (1)	NR	6 (6)	1 (2)
Myalgia	3 (2)	1 (1)	6 (6)	NR
Pain in extremity	7 (5)	7 (9)	15 (15)	2 (4)
Nervous system disorders				
Convulsion	1 (1)	2 (3)	2 (2)	NR
Headache	22 (17)	14 (18)	33 (34)	20 (43)
Respiratory, thoracic and mediastinal disorders				
Cough	5 (4)	1 (1)	9 (9)	8 (17)
Respiratory tract congestion	NR	NR	9 (9)	2 (4)
Skin and subcutaneous tissue disorders				
Rash[a]	8 (6)	6 (8)	11 (11)	2 (4)
Vascular disorders				
Embolism and thrombosis[b]	2 (2)	NR	15 (15)	2 (4)
Deep vein thrombosis	NR	NR	NR	NR
Thrombosis	NR	NR	4 (4)	1 (2)
Hypertension[c]	35 (27)	20 (25)	32 (33)	5 (11)

EPO = epoetin alfa (rch)

NR = not reported

[a]Rash includes urticaria and angioedema

[b]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 (i.e. stroke, including cerebral infarction and cerebral haemorrhage), transient ischaemic attacks and shunt thrombosis (including dialysis equipment) and thrombosis within arteriovenous shunt aneurisms

[c]Hypertension includes hypertensive crisis and hypertensive

Table 3. Summary of Adverse Drug Effects Reported by ≥ 1% of Subjects in Clinical Registration Trials with epoetin alfa (rch): Oncology, HIV, Autologous blood donation, Surgery

System/Organ Class Adverse Drug Effect	Oncology		HIV		Autologous blood donation		Surgery	
	EPO N = 1404 n (%)	Non-ESA N = 930 n (%)	EPO N = 144 n (%)	Placebo N = 153 n (%)	EPO N = 147 n (%)	Non-ESA N = 112 n (%)	EPO N = 213 n (%)	Placebo N = 103 n (%)
Gastrointestinal disorders								
Nausea	265(19)	193(21)	36(25)	39(25)	26(18)	11(10)	96(45)	46(45)
Diarrhoea	168(12)	102(11)	43(30)	51(33)	5(3)	7(6)	18(8)	12(12)
Vomiting	173(12)	134(14)	21(15)	24(16)	7(5)	1(1)	36(17)	14(14)
General disorders and administration site conditions								
Chills	33(2)	32(3)	5(3)	14(9)	8(5)	4(4)	12(6)	1(1)

System/Organ Class Adverse Drug Effect	Oncology		HIV		Autologous blood donation		Surgery	
	EPO N = 1404 n (%)	Non-ESA N = 930 n (%)	EPO N = 144 n (%)	Placebo N = 153 n (%)	EPO N = 147 n (%)	Non-ESA N = 112 n (%)	EPO N = 213 n (%)	Placebo N = 103 n (%)
Influenza like illness	23(2)	10(1)	3(2)	1(1)	4(3)	1(1)	1(< 1)	NR
Injection site reaction	42(3)	31(3)	14(10)	13(9)	NR	1(1)	39(18)	19(18)
Pyrexia	189(13)	130(14)	61(42)	52(34)	7(5)	3(3)	37(17)	27(26)
Peripheral oedema	72(5)	34(4)	7(5)	5(3)	2(1)	2(2)	14(7)	4(4)
Metabolism and nutrition disorders								
Hyperkalaemia	2(< 1)	2(< 1)	NR	NR	NR	NR	NR	1(1)
Musculoskeletal and connective tissue disorders								
Arthralgia	45(3)	43(5)	5(3)	11(7)	3(2)	3(3)	5(2)	3(3)
Bone pain	47(3)	26(3)	3(2)	NR	NR	1(1)	1(< 1)	NR
Myalgia	46(3)	25(3)	8(6)	9(6)	2(1)	3(3)	2(1)	NR
Pain in extremity	37(3)	19(2)	10(7)	13(8)	6(4)	2(2)	7(3)	4(4)
Nervous system disorders								
Convulsion	12(1)	4(< 1)	2(1)	2(1)	NR	NR	NR	NR
Headache	98(7)	50(5)	28(19)	32(21)	17(12)	16(14)	25(12)	9(9)
Respiratory, thoracic and mediastinal disorders								
Cough	98(7)	66(7)	37(26)	22(14)	2(1)	2(2)	10(5)	NR
Respiratory tract congestion	NR	NR	1(1)	NR	NR	NR	NR	NR
Skin and subcutaneous tissue disorders								
Rash[a]	93(7)	47(5)	36(25)	19(12)	3(2)	2(2)	8(4)	2(2)
Vascular disorders								
Embolism and thrombosis[b]	76(5)	33(4)	7(5)	1(1)	6(4)	3(3)	18(8)	6(6)
Deep vein thrombosis	24(2)	6(1)	NR	NR	2(1)	2(2)	10(5)	3(3)
Thrombosis	18(1)	6(1)	NR	NR	2(1)	NR	3(1)	NR
Hypertension[c]	43(3)	24(3)	3(2)	4(3)	NR	2(2)	23(11)	9(9)

EPO = epoetin alfa (rch)

Non-ESA = non-erythropoiesis-stimulating agent

NR = not reported

[a]Rash includes urticaria and angioedema

[b]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 (i.e. stroke, including cerebral infarction and cerebral haemorrhage), transient ischaemic attacks and shunt thrombosis (including dialysis equipment) and thrombosis within arteriovenous shunt aneurisms

[c]Hypertension includes hypertensive crisis and hypertensive

Post-marketing Experience

Adverse drug effects identified during the post-marketing experience with epoetin alfa (rch) are included in Table 4. In the table, the frequencies are provided according to the following convention:

Very common ≥ 1/10

Common ≥ 1/100 and < 1/10

Uncommon ≥ 1/1,000 and < 1/100

Rare ≥ 1/10,000 and < 1/1,000

Very rare < 1/10,000, including isolated reports

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

Table 4. Adverse Drug Effects Identified During Post-marketing Experience with epoetin alfa (rch) by Frequency Category Estimated from Spontaneous Reporting Rates

System/Organ Class	
Frequency	Adverse Drug Effect
Nervous system disorders	
Common	Stroke
Cardiac disorders	
Frequency not known	Mycocardial infarction
Blood and Lymphatic System Disorders	
Very rare	Erythropoietin Antibody-Mediated Pure Red Cell Aplasia Thrombocythaemia

4.9 OVERDOSE

Response to epoetin alfa (rch) is dose-related and individualised. In case of excessive erythropoietic response from an overdose of epoetin alfa (rch), dosing should be stopped and phlebotomy can be considered. Supportive care should be provided for hypertensive or convulsive events that may be related to overdosing with epoetin alfa (rch).

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: antianaemic, ATC code: B03XA01.

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), produced by genetically engineered Chinese hamster ovary cells (rch), has a 165 amino acid sequence identical to that of human urinary EPO; the two are indistinguishable on the basis of functional assays.

The primary pharmacodynamics of Binocrit were assessed *in vitro* using an ELISA, by surface plasmon resonance spectroscopy and by use of a cell-based assay assessing the response to an erythropoietic stimulus. Comparable responses of Binocrit and the reference product epoetin alfa (rch) were obtained.

The biological efficacy of Binocrit has been demonstrated *in vivo* using a normocythaemic mouse assay. After administration of Binocrit, the reticulocyte counts increased similar to the reference product epoetin alfa.

A 5-day *in vivo* pharmacodynamic-pharmacokinetic study in Beagle dogs was performed which used reticulocyte pharmacodynamics as biomarker. After three to four days of Binocrit injection a clear rise in reticulocytes was observed, which was reversible upon cessation of treatment. There was no remarkable difference between Binocrit and the reference product epoetin alfa (rch).

Phase I studies investigating haematological pharmacodynamic parameters following intravenous and subcutaneous single and repeated dosing have demonstrated comparable pharmacodynamics of Binocrit to the reference product epoetin alfa (rch) preparation.

Table 5. Study results from an open, randomized, pivotal IV Phase I study

AUEC	Test medicine (Binocrit)- Epoetin alfa (N=37)	Reference medicine - Epoetin alfa (N=39)	Ratio [%] and 90% CI*
Haemoglobin [g*h/dL]	10056 ± 354	10071 ± 365	99.9 [98.5 – 101.2]
Red blood cells [h/pL]	3322 ± 181	3303 ± 175	100.6 [98.5 – 102.7]
Haematocrit [h]	288 ± 12	289 ± 10	99.6 [98.2 – 101.0]
Reticulocytes [%*h]	1740 ± 186	1788 ± 253	96.8 [92.4 – 101.9]

* based on a parametric approach (ANOVA) for all parameters except for reticulocytes

Table 6. Study results from an open, randomized, pivotal SC Phase I study

AUEC	Test medicine (Binocrit) -Epoetin alfa (N=37)	Reference medicine - Epoetin alfa (N=37)	Ratio [%] and 90% CI*
Haemoglobin [g*h/dL]	10248 ± 494	10469 ± 495	98.9 [97.7 – 100.2]
Red blood cells [h/pL]	3378 ± 184	3511 ± 207	98.7 [97.5 – 99.8]
Haematocrit [h]	300 ± 14	308 ± 13	98.7 [97.3 – 100.0]
Reticulocytes [%*h]	1525 ± 267	1660 ± 274	93.4 [88.3 – 98.8]

* based on a parametric approach (baseline-adjusted ANCOVA)

A randomised, double-blind, multi-centre phase III study (study number 2003-29-INJ-9) was conducted to evaluate therapeutic equivalence in terms of haemoglobin response of Binocrit versus the reference product epoetin alfa (rch) in the long-term intravenous treatment of anaemia in haemodialysis patients after a 1:1 dose conversion from reference product epoetin alfa (rch) to Binocrit. The study included 478 haemodialysis patients with CRF that were treated with the reference product at time of inclusion to the study.

In the first part (double-blind) of the study patients were randomly assigned to continue treatment with their original therapy (N = 164) or to switch to Binocrit (N = 314).

In the evaluation phase (weeks 25-28) patients treated with Binocrit showed a comparable Hb-level after treatment with Binocrit to their Hb-level at start of the treatment. No relevant differences regarding dosing could be observed. Binocrit has shown to be therapeutically equivalent to reference product epoetin alfa (rch) with respect to Hb response in haemodialysis patients after a 1:1 switch.

In the second (open) part of the study patients of the reference group were changed to Binocrit and treated for another 28 weeks. The switch to Binocrit did not demonstrate any safety relevant changes.

The long-term safety profiles of Binocrit and reference medicine epoetin alfa (rch) were comparable. No formation of anti-epoetin antibodies was detected. The safety and efficacy of subcutaneous administration of Binocrit in patients with chronic renal failure has not been studied.

A randomised, double-blind, multi-centre phase III study (study number 2003-31-INJ-11) was conducted to assess the efficacy and safety of Binocrit in the treatment of chemotherapy-induced, symptomatic anaemia in patients with solid tumours.

114 patients were treated with Binocrit or reference medicine epoetin alfa (rch) three times a week subcutaneously for 12 weeks. Doses were raised in case of insufficient increase of Hb respectively reticulocytes after 4 or 8 weeks.

In 62% of patients under Binocrit treatment the Hb level increased by ≥ 20 g/L with the confidence interval being entirely above the predefined threshold of 30%. In the Binocrit group, 32% of patients required transfusions versus 38% in the reference medicine epoetin alfa (rch) group. None of the secondary efficacy endpoints showed relevant differences between the treatment groups and also the safety profiles were similar.

Binocrit was shown to be efficacious in the treatment of chemotherapy-associated anaemia in solid tumour patients with a safety profile not differing from what is expected in this therapeutic area.

Binocrit has not been studied in patients scheduled for elective surgery, either to treat moderate anaemia or to augment autologous blood collection (see Section 4.1 Therapeutic indications). However, comparable efficacy and safety can be expected in these patients since comparable efficacy and safety to reference medicine epoetin alfa (rch) has been demonstrated in the anaemia of chronic renal failure (IV administration) and chemotherapy-induced anaemia settings.

5.2 PHARMACOKINETIC PROPERTIES

Erythropoietin stimulates erythropoiesis in anaemic patients with chronic renal failure in whom the endogenous production of erythropoietin is impaired. Because of the length of time required for erythropoiesis - several days for erythroid progenitors to mature and be released into the circulation - a clinically significant increase in haemoglobin is usually not observed in less than two weeks and may require up to ten weeks in some patients.

Measurement of epoetin alfa (rch) following intravenous administration showed 10% excretion by the kidneys with the major routes of elimination not determined. After intravenous administration, the mean half lives in normal volunteers ranged from 4.0 to 6.1 hours and in patients with chronic renal failure from 6.5 to 9.3 hours. Following subcutaneous injection, serum levels are much lower than the levels achieved following IV injection; the levels increase slowly and reach a peak between 12 and 18 hours post-dose.

The peak is always well below the peak achieved using the IV route (approximately 1/20th of the value). Following subcutaneous injection, erythropoietin serum levels remain elevated above baseline for about 72 hours. There is no accumulation when thrice weekly dosing is used: the levels remain the same, whether they are determined 24 hours after the first injection or 24 hours after the last injection. The half-life is difficult to evaluate for the subcutaneous route and is estimated about 24 hours. The bioavailability of subcutaneous injectable erythropoietin is much lower than that of the intravenous drug: approximately 20-30%. No information is available in the young and in the elderly. Due to decreased metabolism, patients with hepatic dysfunction may have increased erythropoiesis with epoetin alfa (rch).

Erythropoiesis-stimulating agents (ESAs) are growth factors that primarily stimulate red cell production. Erythropoietin receptors may be expressed on the surface of a variety of tumour cells.

Bioequivalence. Phase I studies investigating pharmacokinetic parameters following intravenous and subcutaneous repeated dosing have demonstrated the bioequivalence of Binocrit to the reference medicine epoetin alfa (rch) preparation.

Bioequivalence after multiple intravenous administration was demonstrated in an open, randomised, parallel study in 80 healthy volunteers receiving 100 IU/kg body weight 3 times per week for 4 weeks. The pharmacokinetic parameters are summarised below.

	Ratio	90% Confidence interval	Mean±SD [Test Medicine (Binocrit) - Epoetin alpha (rch)]	Mean ± SD [Reference Medicine- Epoetin alfa (rch)]
C_{max}	97.5%	91.1 – 104.5	2189 mIU/mL ± 393.7	2262 mIU/mL ± 422.0
AUC	89.2%	82.5 – 96.2	8422 mIU/mL·h ± 2419	9224 mIU/mL·h ± 1850
$t_{1/2}$	87.8%	75.3 – 100.0	4.14h ± 1.71	4.74h ± 2.00

Bioequivalence after multiple subcutaneous administration was demonstrated in an open, randomised, parallel study in 80 healthy volunteers receiving 100 IU/kg body weight 3 times per week for 4 weeks. The pharmacokinetic parameters are summarised below.

	Ratio	90% Confidence interval	Mean±SD [Test Medicine (Binocrit) - Epoetin alpha (rch)]	Mean ± SD [Reference Medicine - Epoetin alfa (rch)]
C_{max}	97.6%	84.2 – 113.1	82.410 mIU/mL ± 48.69	82.817 mIU/mL ± 34.06
AUC	96.9%	88.2 – 106.5	2044.9 mIU/mL·h ± 587.9	2095.0 mIU/mL·h ± 486.4
$t_{1/2}$	97.9%	81.0 – 118.2	18.28h ± 8.50	18.16h ± 7.52

These results demonstrate that Binocrit is bioequivalent to the reference medicine epoetin alfa (rch) preparation with respect to the pharmacokinetic parameters AUC and C_{max} after multiple intravenous and multiple subcutaneous application.

5.3 PRECLINICAL SAFETY DATA

Carcinogenesis, mutagenesis

Long-term carcinogenicity studies have not been carried out. There are conflicting reports in the literature regarding whether erythropoietins may play a role as tumour proliferators.

These reports, based on *in vitro* findings from human tumour samples, are of uncertain significance in the clinical situation. In a standard series of assays for genotoxic potential, epoetin alfa (rch) did not induce gene mutations or cause chromosomal damage.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Binocrit contains the following inactive ingredients: sodium dihydrogen-phosphate dihydrate, disodium hydrogen-phosphate dihydrate, sodium chloride, glycine, polysorbate 80, nitrogen and water for injection. Hydrochloric acid and sodium hydroxide may be used for pH adjustment.

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

24 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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

When the product is about to be used, it may be removed from the refrigerator and stored at room temperature (below 25ºC) for a maximum single period of three days.

The product should not be used, and discarded

- if the seal is broken,
- if the liquid is coloured or you can see particles floating in it,
- if you know, or think that it may have been accidentally frozen, or
- if there has been a refrigeration failure.

6.5 NATURE AND CONTENTS OF CONTAINER

1 pre-filled syringe per pack.

6 pre-filled syringes per pack.

1 pre-filled syringe per pack with a needle safety guard.

6 pre-filled syringes per pack with a needle safety guard.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Novartis New Zealand Limited
PO Box 99102
Newmarket
Auckland 1149

Telephone: 0800 354 335

9 DATE OF FIRST APPROVAL

19 April 2012

10 DATE OF REVISION OF THE TEXT

10/08/2020

NEW ZEALAND DATA SHEET

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
Boxed Warning	Addition for use of cancer.
All	Minor editorial changes made throughout.
4.1	Revision on indication on treatment of anaemia and where blood transfusion is not considered appropriate.