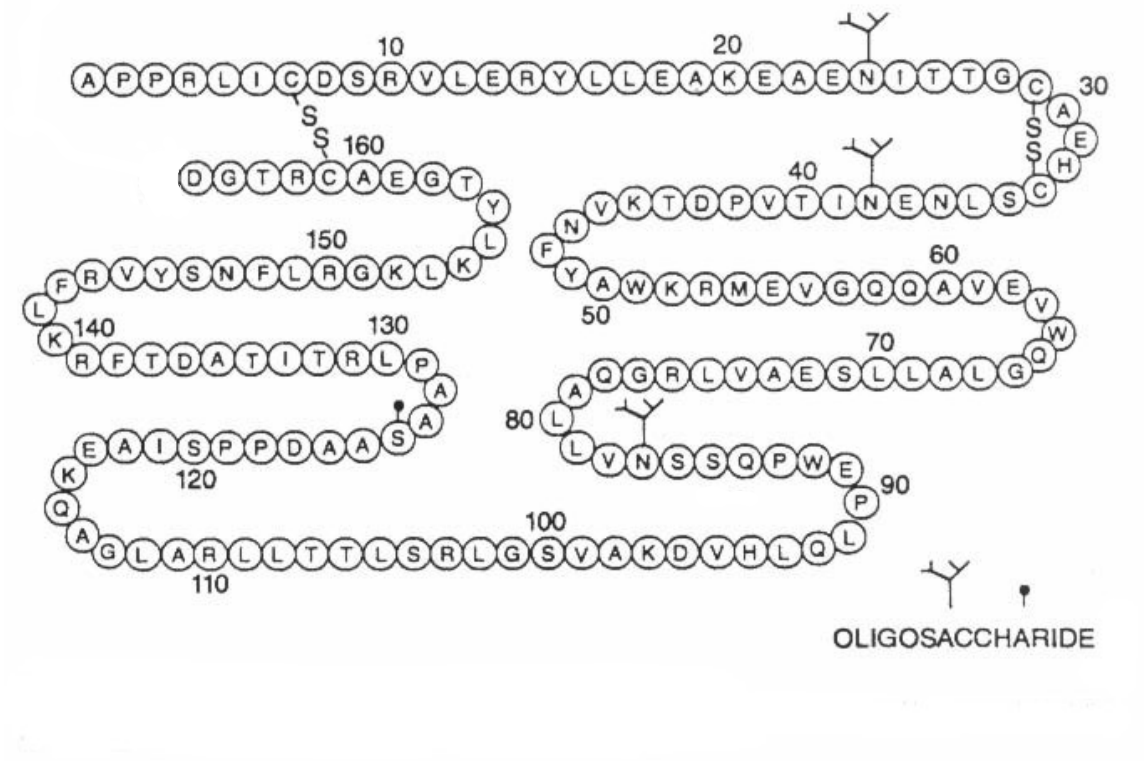
NAME OF THE MEDICINE

NEORECORMON®

Epoetin beta rch (recombinant human erythropoietin)



CAS registry number: 122312-54-3

DESCRIPTION

NEORECORMON (epoetin beta *rch*) is a sterile, purified, stable recombinant human erythropoietin concentrate produced from genetically engineered chinese hamster ovary (CHO) cells containing a cloned human erythropoietin gene.

The active ingredient, epoetin beta *rch*, is a highly purified glycoprotein, identical in amino acid sequence to endogenous erythropoietin, with a mean molecular weight of approximately 30kDa. Epoetin beta *rch* is ≥ 98% pure, with no detectable cell line residues.

NEORECORMON is available in pre-filled syringes containing the excipients urea, sodium chloride, sodium phosphate - monobasic, sodium phosphate - dibasic, calcium chloride, polysorbate 20, glycine, leucine, isoleucine, threonine, glutamic acid and phenylalanine.

PHARMACOLOGY

Pharmacodynamics

Epoetin beta is a glycoprotein that stimulates the proliferation and differentiation processes of the erythroid stem cell compartment and also has a stimulatory effect on the proliferation and maturation compartment of the erythron. Epoetin beta therefore leads to an increase in haemoglobin formation and an associated acceleration of cell maturation with reduction in the

cell cycle time. A further effect of epoetin beta is the acceleration of reticulocyte maturation and an increase in the release of reticulocytes into the bloodstream.

Pharmacokinetics

Absorption

Subcutaneous administration of epoetin beta *rch* results in variable rates of absorption with average maximal concentrations being reached between 12 and 28 hours after dosing.

Distribution

The distribution volume of epoetin beta *rch* administered intravenously corresponds to 1–2 times the plasma volume.

Elimination

The half-life of intravenously administered epoetin beta *rch* is between 4 and 12 hours. The protracted absorption of subcutaneously administered epoetin beta *rch* results in an apparent terminal half-life of between 13 and 28 hours.

Bioavailability

The bioavailability of subcutaneously administered epoetin beta *rch* is between 23% and 42% as compared with intravenous administration. Slightly higher bioavailability occurs on repeated subcutaneous administration.

CLINICAL TRIALS

The therapeutic efficacy of epoetin beta *rch* has been evaluated in renal anaemia, autologous blood donation prior to elective surgery, the prevention of renal anaemia in premature infants and the treatment of anaemia in patients with non-myeloid malignancies.

Anaemic Patients with Chronic Kidney Disease (CKD)

Adult patients with renal anaemia on haemodialysis, peritoneal dialysis or not yet undergoing dialysis (pre-dialysis) and uraemic children were studied.

Increases in reticulocyte count and haematocrit were observed from the first and second week respectively. With the recommended dose regimens, an increase in haematocrit of approximately 0.5%–1.0% per week is to be expected. The time to reach a target haematocrit was dependent on the baseline haematocrit and on the dose of epoetin beta *rch* used. The target haematocrit was reached by most patients after 12 weeks. The need for regular transfusions was abolished much earlier, usually after 4 weeks of therapy. Considerable improvements in physical performance and well-being were reported in most patients treated with epoetin beta *rch*. Overall the therapeutic effects were fairly similar, irrespective of whether patients were on haemodialysis, peritoneal dialysis or not yet undergoing dialysis (pre-dialysis patients). The maintenance doses required were approximately 25%–30% lower if epoetin beta *rch* was given subcutaneously rather than intravenously.

In children response rates were age-dependent. Younger patients required more time and higher doses to reach target haematocrit. Most children reached the target haematocrit after 3 months and transfusions were abolished after 1 month if high enough doses were given. Although the response in children was age-dependent, the recommendations for the starting doses are the same for adults and children.

A summary of pivotal trials conducted in anaemic CKD patients is shown below in Table 1.

Table 1. Summary of pivotal trials in anaemic CKD patients

Study/ Design	Patient numbers	Diagnosis	Duration	Epoetin beta dose/ route of administration	Efficacy results
MF 3981 R, B, P	129 Epo = 63 P = 66	Long term haemodialysis Hct ≤ 28%, ≥ 4 transfusions in last year	6 months	Correction: 80 IU/kg i.v. 3 x wk Maintenance: 40 IU/kg i.v 3 x wk then based on Hct	Hct increase/wk Epo: 0.91 vol.%, P: 0.15 vol.% (*p < 0.0001*) Transfusion frequency Epo: 10%, P: 41% (*p < 0.001*)
MF 4135 R, O, U	361 Safety: Epo = 181 U = 180 Efficacy Epo = 170 U = 168	Long term haemodialysis Hct ≤ 28% or transfusion 4 weeks before randomisation	1 year	Correction: 20 IU/kg s.c. 3 x wk for 6 weeks, inc. as needed Maintenance: 50% correction dose then adj. based on Hct	Hb increase (change from baseline at one year) Epo: + 26 g/L U: + 5 g/L Transfusion frequency (month 1) Epo: 14%, U: 30% Average maintenance dose at year 1: 93 IU/kg/wk

B = double blind, O = open label, P = placebo control group, R = randomised, U = untreated control group,
Epo = epoetin beta *rch*, Hct = haematocrit, Hb = haemoglobin, i.v. = intravenous, s.c. = subcutaneous

Haemoglobin levels were effectively maintained in CKD patients switched from two or three times weekly to once weekly subcutaneous epoetin beta *rch* administration, and in patients switched from once weekly to once every two weeks administration.

Autologous Pre-Donation

Treatment is indicated in patients with moderate anaemia [packed cell volume (PCV) approximately 33%–39% (Hb approx. 110–130 g/L) no iron deficiency] if blood conserving procedures are not available or insufficient either;

- when the scheduled major elective surgery requires a large volume of blood (4 or more units for females or 5 or more units for males), or
- when the period necessary to obtain the required volume of blood is too short.

The efficacy of epoetin beta *rch* in an autologous blood donation programme was demonstrated by the gain in red cell volume available at the time of surgery. The period of anaemia after blood donation was shortened and, postoperatively, haematocrit values moved towards initial values much more rapidly in epoetin beta *rch* than in placebo patients. The effective doses ranged between 200–800 IU/kg twice weekly i.v. and 150–600 IU/kg twice weekly s.c.

Individual dose recommendations for epoetin beta *rch* in this indication are necessary and can be calculated from the nomograms taking into account the endogenous red cell reserve, the amount of autologous blood required and the sex of the patient. The nomograms also determine if the patient could donate sufficient amount of blood even without NEORECORMON treatment.

Table 2. Summary of pivotal trial in patients scheduled for elective surgery

Study / Design	Patient numbers	Diagnosis	Duration	Epoetin beta dose	Efficacy results
MF 4312 R, O, U	105 Epo = 50 U = 47	Total hip surgery	3 weeks	500 IU/kg x 2/wk s.c.	Blood loss both groups 1 L Blood transfusion (all) Epo: 46.0%, U: 88.9% ($p < 0.0001$) Blood transfusion (homologous) Epo: 10.0%, U: 35.6% ($p = 0.0054$)

R = randomised, O = open label, U = untreated control group, Epo = epoetin beta *rch*, s.c. = subcutaneous

Anaemia of Prematurity

The effectiveness of epoetin beta *rch* in the prevention of anaemia of prematurity was shown with a higher percentage of infants not needing transfusions in the epoetin beta *rch* group as compared with the untreated control group. In addition, the blood volumes transfused and the number of transfusions were lower in epoetin beta *rch* treated infants.

The success rates (haematocrit permanently > 32% without transfusions) were significantly higher in the epoetin beta *rch* group than in the control group. However, there are certain prognostic factors for successful results. Whereas infants with birth weight > 1100 g and baseline haematocrit > 45% benefited most, no success was achieved in those with both a birth weight < 1100 g and a baseline haematocrit < 45%.

Table 3. Summary of pivotal trial in the prevention of anaemia of prematurity

Study / Design	Patient numbers	Diagnosis	Duration	Epoetin beta dose	Efficacy results
MF 4268 R, B, U	241 Epo = 120 U = 121	Premature infants with 750–1499 g birth weight	38–40 days	250 IU/kg x 3/wk s.c.	Success rate: Epo: 27.5%, U: 4.1% ($p < 0.0077$) Transfusion rate: Epo: 50%, U: 67% ($p = 0.009$)

R = randomised, B = double blind, U = untreated control group, Epo = epoetin beta *rch*, s.c. = subcutaneous

Anaemia in Patients with Non-Myeloid Malignancies

The effectiveness of epoetin beta *rch* was established in patients with solid tumours and lymphoid malignancies. In patients with solid tumours, epoetin beta *rch* was shown to increase haemoglobin levels or reduce the development of anaemia induced by chemotherapy and significantly reduce the need for blood transfusions. In patients with lymphoid malignancies, epoetin beta *rch* was shown to increase haemoglobin levels and significantly reduce the need for blood transfusion. Response rate (defined as an increase of 20 g/L from baseline without need for transfusion in the preceding 6 weeks) was significantly greater in epoetin beta *rch* treated patients than placebo and median time to first response was significantly shorter in the epoetin beta *rch* treated groups. For the patients who showed a response to treatment, the improvement in haematological parameters was associated with a statistically significant corresponding improvement in the patients' self-assessment of their quality of life.

Clinical studies have shown the efficacy of epoetin beta *rch* administered once weekly is similar to that of the thrice weekly regimen.

Table 4. Summary of pivotal trials for anaemia in patients with non-myeloid malignancies

Study / Design	Patient numbers	Diagnosis	Duration	Epoetin beta dose	Efficacy results
MF 4249 R, O, U	120 Epo = 87 U = 33	Ovarian carcinoma stage IIb to IV* and Hb < 130 g /L	Up to 24 weeks	150 or 300 IU/kg, x 3 /wk s.c.	At least one transfusion: Epo: 9.2%, U: 39% (*p = 0.0002)* No greater efficacy with 300 IU/kg x 3 /wk than 150 IU/kg x 3 /wk
MF 4321 R, O, U	218 Epo = 114 U = 104	Various solid tumours treated with chemotherapy*	Up to 24 weeks	5000 IU/day s.c.	At least one transfusion: Epo: 28.1%, U: 45.3% (*p = 0.013* logrank test)
MF 4467 R, B, P	343 Epo = 170 P = 173	MM, NHL or CLL anaemia (Hb < 100 g/L) transfusion dependent erythropoietin deficiency (O/P ratio < 1.0)	16 weeks	150 IU x 3 /wk s.c. adjusted according to Hb	At least one transfusion: Epo: 33.3%, P: 52.4% (*p = 0.0012*) Percentage of responders Epo: 67%, P: 27% (*p = 0.0001*) Median time to response (weeks) Epo: 9, P: >16 (*p = 0.0001*) Improved quality of life in epoetin beta treated group
MF 4421 R, O, S	262 Epo = 133 S = 129	50% various solid tumours + 55% lymphoid malignancies	12 weeks	150 IU/kg x 3 /wk	Significant improvement in QoL with Epo (*p = 0.001* for FACT-F, *p = 0.01* for SF36 PCS and *p = 0.068* for FACT-An). Hb response (Increase in Hb > 20g/L without transfusion) Epo: 47%, S: 13% (*p = 0.001*) Benefits were observed irrespective of tumour type or chemotherapy regimen

R = randomised, O = open label, U = untreated control group, B = double blind, P = placebo control group, S = standard care (anti-tumour therapy + blood transfusion as required), Epo = epoetin beta *rch*, MM = multiple myeloma, NHL = Non-Hodgkin's lymphoma (low-grade), CLL = Chronic lymphocytic leukaemia, O/ = (observed serum erythropoietin concentration) /P = (predicted serum erythropoietin concentration), QoL = quality of life, FACT-F = Functional Assessment of Cancer Therapy (fatigue scale), FACT-An = Functional Assessment of Cancer Therapy (anaemia scale), PCS = physical component summary, * + platinum based chemotherapy

INDICATIONS

NEORECORMON is indicated;

- for the treatment of anaemia associated with chronic kidney disease (CKD) in patients on dialysis and symptomatic patients not yet undergoing dialysis,
- to increase the yield of autologous blood from patients in a pre-donation programme initiated to avoid the use of homologous blood,
- for the prevention of anaemia of prematurity in infants with a birth weight of 750 g to 1500 g and a gestational age of less than 34 weeks,
- for the treatment of anaemia and reduction of transfusion requirements in patients with non-myeloid malignancies, where anaemia develops as a result of concomitantly administered chemotherapy.

CONTRAINDICATIONS

NEORECORMON is contraindicated in patients with;

- poorly controlled hypertension,
- known hypersensitivity to the active substance or any of the excipients.

In the indication "increasing the yield of autologous blood" NEORECORMON must not be used in patients who, in the month preceding treatment, have suffered a myocardial infarction or stroke, patients with unstable angina pectoris, or patients who are at risk of deep venous thrombosis such as those with a history of venous thromboembolic disease.

PRECAUTIONS

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 (ESAs) such as NEORECORMON.

In controlled clinical trials ESAs increased the risk for death in oncology patients and for serious cardiovascular events in oncology and CKD patients when administered to target a haemoglobin of > 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 > 10 g/L over 2 weeks may also contribute to these risks.

To reduce cardiovascular risks, use the lowest dose of NEORECORMON that will gradually increase the haemoglobin concentration. The haemoglobin concentration should not exceed 120 g/L and the rate of haemoglobin increase should not exceed 10 g/L in a 2-week period. Haemoglobin levels should be checked at regular intervals and dosages adjusted (see DOSAGE and ADMINISTRATION).

The use of NEORECORMON during an autologous blood pre-donation programme must be balanced against the reported increased risk of thromboembolic events. Patients in an autologous blood pre-donation programme prior to surgery, including orthopaedic surgery, who have been treated with NEORECORMON, had a higher incidence of thromboembolic events (6.7%), compared with placebo-treated patients (3.4%).

Growth Factor Potential / Increased Tumour Progression

NEORECORMON, like other ESAs, is a growth factor that primarily stimulates red blood cell production. As with all growth factors, there is a theoretical concern that ESAs could act as a growth factor for any type of malignancy. ESAs, when administered to target haemoglobin of > 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 of > 120 g/L.

Use in Cancer Patients

A study comparing another ESA (epoetin alfa) with placebo in cancer patients with anaemia who were not being treated with chemotherapy demonstrated no benefit in terms of reduced transfusion requirements. In addition, there were an increased number of deaths in the active group (26% vs. 20%). NEORECORMON should only be used to treat cancer patients with anaemia where the anaemia has arisen as a result of concomitantly administered chemotherapy.

Hypertension

Patients with uncontrolled hypertension should not be treated with NEORECORMON; blood pressure should be controlled adequately before initiation of therapy. Blood pressure may rise during treatment of anaemia with NEORECORMON. Hypertensive encephalopathy and seizures

have been observed. They require the immediate attention of a physician and intensive medical care. Particular attention should be paid to sudden stabbing migraine-like headaches as a possible warning sign.

Special care should be taken to closely monitor and control blood pressure in patients treated with NEORECORMON. During NEORECORMON therapy, patients should be advised of the importance of compliance with anti-hypertensive therapy and dietary restrictions. If blood pressure is difficult to control after initiation of appropriate measures, the dose of NEORECORMON should be reduced or temporarily withheld until haemoglobin begins to decrease (see DOSAGE and ADMINISTRATION).

Pure Red Cell Aplasia (PRCA)

PRCA caused by neutralising anti-erythropoietin antibodies has been reported in association with ESA therapy, including NEORECORMON. These antibodies have been shown to cross-react with all erythropoietic proteins, and patients suspected or confirmed to have neutralising antibodies to erythropoietin should not be switched to NEORECORMON. If anti-erythropoietin antibody-mediated PRCA develops whilst on NEORECORMON, therapy with NEORECORMON must be discontinued and patients should not be switched to another ESA.

Seizures

ESAs should be used with caution in patients with epilepsy. Convulsions have been reported in patients with CKD receiving NEORECORMON.

General

In order to improve the traceability of biological medicinal products, the trade name of the administered product should be clearly recorded in the patient medical record. Substitution by any other biological medicinal product requires the consent of the prescribing physician.

NEORECORMON should be used with caution in the presence of refractory anaemia with excess blasts in transformation, thrombocytosis, and chronic liver failure.

NEORECORMON contains phenylalanine as an excipient therefore this should be taken into consideration in patients affected with severe forms of phenylketonuria.

Anaphylactoid reactions have been observed in isolated cases. Rarely, skin reactions such as rash, pruritus, urticaria or injection site reactions may occur, however in controlled clinical studies, no increased incidences of hypersensitivity reactions were found. It is recommended that the first dose be administered under medical supervision.

The indication of nephrosclerotic patients not yet undergoing dialysis should be defined individually as a possible acceleration of progression of renal failure cannot be ruled out with certainty.

In dialysis patients, an increase in heparin dose is frequently required during the course of NEORECORMON therapy as a result of increased haemoglobin. Occlusion of the dialysis system is possible if heparinisation is not optimum. Shunt thrombosis may occur, especially in patients who have a tendency to hypotension or whose arteriovenous fistulae exhibit complications (e.g. stenoses, aneurysms). Early shunt revision and thrombosis prophylaxis by administration of acetylsalicylic acid, for example, is recommended in these patients.

Misuse by healthy persons may lead to an excessive increase in haemoglobin. This may be associated with life-threatening complications to the cardiovascular system (see Cardiovascular and Thrombotic Events).

Effects on Laboratory Tests

Platelet counts
There may be a moderate dose-dependent rise in the platelet count, within the normal range, during treatment with NEORECORMON, especially after intravenous administration. This regresses during continued therapy. Development of thrombocytosis is very rare. It is recommended that the platelet count is regularly monitored during the first eight weeks of therapy. In autologous blood donation, treatment with NEORECORMON should be discontinued if platelets rise above the normal range or increase by more than 150×10^9/L.

Potassium and phosphate levels
Serum potassium and phosphate concentrations should be monitored regularly during NEORECORMON therapy. Potassium elevation has been reported in a few uraemic patients receiving NEORECORMON although causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to ceasing NEORECORMON administration until the level has been corrected.

Transient increases in serum phosphate levels have been observed in isolated cases in CKD patients.

Lack of Effect

The most common reasons for an incomplete response to ESAs are iron deficiency and chronic inflammation (e.g. access infections, surgical inflammation, AIDS, SLE). The following conditions may also compromise the effectiveness of ESA therapy: chronic blood loss, bone marrow fibrosis, severe aluminium overload due to treatment of renal failure, folic acid or vitamin B_{12} deficiencies, and haemolysis. If all the conditions mentioned are excluded and the patient has a sudden drop of haemoglobin associated with reticulocytopenia and anti-erythropoietin antibodies, examination of the bone marrow for the diagnosis of PRCA should be considered. If PRCA is diagnosed, therapy with NEORECORMON must be discontinued and patients should not be switched to another ESA (see PRCA).

Evaluation of Iron Status

In order to ensure effective erythropoiesis, iron status should be evaluated for all patients before and during treatment, as the majority of patients will eventually need supplemental iron. *As per CARI* (Caring for Australasians with Renal Impairment) Guidelines, supplemental iron therapy is recommended for all CKD patients whose serum ferritin falls below 100 ng/mL or transferrin saturation below 20%.

In premature infants, oral Fe^{2+} should begin as soon as possible (by day 14 of life at the latest) at a dose of 2 mg/day. If serum ferritin falls below 100 ng/mL or if there are other signs of iron deficiency, the Fe^{2+} dose should be increased to 5–10 mg/day.

Autologous Pre-Donation

For the use of NEORECORMON in an autologous pre-donation programme, the official guidelines on principles of blood donation must be considered. In particular;

- only patients with a PCV ≥ 33 % or Hb ≥ 110 g/L should donate,
- special care should be taken with patients whose weight is below 50 kg,
- the single blood volume drawn should not exceed approximately 12% of the patient's estimated blood volume.

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) treatment should only be given to patients with no

iron deficiency and if blood conserving procedures are not available or insufficient. Treatment should be reserved for patients in whom it is considered of particular importance to avoid homologous blood transfusion taking into consideration the risk/benefit assessment for homologous transfusions.

Use in Premature Infants

Prognostic factors for successful results are infant birth weight and baseline haematocrit (Hct). Infants with both a birth weight > 1100 g and baseline Hct > 45% benefited most. No success was achieved in those infants with both a birth weight < 1100 g and baseline Hct < 45%.

Lack of efficacy in terms of success rate (i.e. failure to maintain PCV permanently > 32% without blood transfusion) was observed in infants with lower birth weight i.e. < 1100 g. Nevertheless, in this subgroup, 8 of the 33 infants on epoetin beta *rch* but only 2 of the 29 in the control group completed the study without needing transfusions.

Use in Pregnancy - Category B3

Epoetin beta *rch* was not teratogenic in rats and rabbits at doses of up to 3000 IU/kg/day i.v. when administered during the period of organogenesis. Epoetin beta *rch* caused post-implantation loss and decreased foetal weight in animals dosed prior to mating right through gestation at doses of 160 U/kg/day s.c. and above. Kinked tails were observed in rat pups and foetuses (from 160 U/kg s.c. upwards). These effects are thought to be related to the pharmacodynamic action of the drug.

All safety information with regards to exposure of NEORECORMON during pregnancy have been gained from post marketing experience. A review of the available post marketing data does not show evidence of a causal association between harmful effects with respect to pregnancy, embryonal/foetal development or postnatal development and treatment with NEORECORMON. However in the absence of clinical study data, caution should be exercised when prescribing to pregnant women.

Use in Lactation

Postnatal observations of the live offspring (F_1 generation) of female rats treated with epoetin beta *rch* during gestation and lactation revealed no effect of epoetin beta *rch* at doses up to 1280 U/kg s.c. There were, however, decreases in body weight gain, eyelid opening, and delayed testicular descent and vaginal opening in the F_1 foetuses at doses of 320 IU/kg s.c. and above.

Only limited experience in human lactation has been gained. Endogenous erythropoietin is excreted into breast milk but it is not known whether it is absorbed by the neonatal gastrointestinal tract in functional form. A decision on whether to continue or discontinue breast-feeding or to continue or discontinue therapy with NEORECORMON should be made taking into account the benefit of breast-feeding to the child and the benefit of NEORECORMON therapy to the woman.

Paediatric Use

Clinical trials have been performed in children and adolescents with anaemia due to chronic kidney disease (CKD) and in neonates for prevention of anaemia due to prematurity. For CKD, NEORECORMON should not be used in infants (i.e. below 2 years of age). NEORECORMON is not indicated for paediatric patients to increase autologous blood yield; nor for anaemic paediatric patients with non-myeloid malignancies receiving chemotherapy.

Use in the Elderly

No dedicated studies in elderly patients have been performed. A large proportion of elderly patients were included in clinical trials with NEORECORMON, however, a need for special dose adjustments in the elderly population has not been studied.

Carcinogenicity

Since epoetin beta is a human protein and as such is immunogenic for other species, conventional 2-year carcinogenicity studies have not been undertaken in rodents. A carcinogenicity study with homologous erythropoietin in mice did not reveal any signs of proliferative or tumourigenic potential.

Mutagenicity

Epoetin beta *rch* did not reveal any genotoxic potential in a series of assays for gene mutations (Ames test, chinese hamster lung cells) or chromosomal damage (human lymphocytes *in vitro*, mouse micronucleus test *in vivo*).

Impairment of Fertility

No fertility studies have been conducted in humans. However, epoetin beta *rch* at doses of up to 640 U/kg/day s.c. did not affect fertility in rats.

Effects on Ability to Drive and Operate Machinery

No effects on ability to drive or use machines have been observed.

INTERACTIONS WITH OTHER MEDICINES

Clinical results to date do not indicate any interaction with other substances.

ADVERSE EFFECTS

Anaemic Patients with Chronic Kidney Disease (CKD)

The most frequent adverse drug reactions (common 1-10%), in particular during the early treatment phase with NEORECORMON are hypertensive events. Increases in blood pressure can occur in normotensive patients or can be an aggravation of existing hypertension (see PRECAUTIONS).

From controlled clinical trials in 490 patients (244 epoetin beta *rch*, 246 control) the following adverse reactions were reported in > 5% of patients.

Table 5. Incidence of adverse reactions in anaemic CKD patients

Adverse Reactions	Incidence in Epoetin Beta Group [n =244] (%)	Incidence in Control Group [n =246] (%)
At least one adverse reaction	76.2	73.6
Cardiovascular		
Hypertension	23.4	11.4
Cardiocirculatory failure	4.5	5.7
Vascular access problems		
Shunt thrombosis	8.2	8.5
Respiratory		
Upper respiratory tract infection	12.7	8.5
Lower respiratory tract infection	8.6	11.4

Adverse Reactions	Incidence in Epoetin Beta Group [n =244] (%)	Incidence in Control Group [n =246] (%)
Body as a whole		
Infections	5.7	4.5
Musculoskeletal		
Joint and limb disorders	7.0	5.3
Urogenital		
Menstrual disorders	9.1	4.1
Digestive		
Liver enzymes increased	5.3	6.5
Metabolic and nutritional disorders		
Hyperkalaemia	7.0	4.9
Overhydration	7.0	4.9
Skin		
Injection site	5.7	-

Cardiovascular System: *Common* (> 1%): headache; *Uncommon* (0.1 ≤ 1%): hypertensive crisis with encephalopathy-like symptoms (e.g. headaches and confused state, sensorimotor disorders - such as speech disturbance or impaired gait - up to tonoclonic seizures).

Blood: *Common* (> 1%): decrease of ferritin values and transferrin saturation; *Uncommon* (0.1 ≤ 1%): vascular access thromboses in hypotensive patients or those with vascular access complications, increase in platelet count; *Very rare* (< 0.01%): thrombocytosis, transient increase in potassium and phosphate.

Increasing the Amount of Autologous Blood

From clinical trials in 458 patients (341 epoetin beta *rch*, 117 control) the following adverse reactions were reported in > 5% of patients.

Table 6. Incidence of adverse reactions when increasing the amount of autologous blood

Adverse Reactions	Incidence in Epoetin Beta Group [n =341] (%)	Incidence in Control Group [n =117] (%)
At least one adverse reaction	50.7	35.0
Cardiovascular		
Coronary heart diseases	9.7	5.1
Respiratory		
Upper respiratory tract infection	5.0	1.7
Central nervous system		
Dizziness	6.5	5.1
Body as a whole		
Asthenia	5.9	1.7

Anaemia of Prematurity

From clinical trials in 404 patients (213 epoetin beta *rch*, 191 control) the following adverse reactions were reported in > 5% of patients.

Table 7. Incidence of adverse reactions in premature anaemic infants

Adverse Reactions	Incidence in Epoetin Beta Group [n =213] (%)	Incidence in Control Group [n =191] (%)
At least one adverse reaction	20.2	24.6
Body as a whole		
Sepsis	5.6	4.7
Blood		
Leukopenia	3.3	6.3

Anaemia in Patients with Non-Myeloid Malignancies

From clinical trials in 335 patients (198 epoetin beta *rch*, 137 control) the following adverse reactions were reported in > 5% of patients with solid tumours.

Table 8. Incidence of adverse reactions in anaemic patients with solid tumours

Adverse Reactions	Incidence in Epoetin Beta Group [n =198] (%)	Incidence in Control Group [n =137] (%)
At least one adverse reaction	71.2	61.3
Blood		
Leukopenia	31.3	19.0
Thrombocytopenia	20.7	7.3
Anaemia general	2.0	5.8
Digestive		
Nausea and vomiting	29.8	16.8
Indigestion	5.6	4.4
Body as a whole		
Malignancy progression	14.1	20.4
Asthenia	6.6	5.1
Pyrexia	5.6	5.1
Urogenital		
Urinary tract infections	6.1	-

From clinical trials in 343 patients (170 epoetin beta *rch*, 173 control) the following adverse reactions were reported in > 5% of patients with haematological tumours (MM, NHL, CLL).

Table 9. Incidence of adverse reactions in anaemic patients with haematological tumours

Adverse Reactions	Incidence in Epoetin Beta Group [n =170] (%)	Incidence in Control Group [n =173] (%)
At least one adverse reaction	71.8	76.3
Body as a whole		
Malignancy progression	21.8	21.4
Fever	6.5	9.8
Cardiovascular system		
Hypertension	9.4	5.2
Haemic and lymphatic system		
Leukopenia	8.2	5.2
Thrombocytopenia	8.8	2.9

Adverse Reactions	Incidence in Epoetin Beta Group [n =170] (%)	Incidence in Control Group [n =173] (%)
Respiratory system		
Upper respiratory infection	11.2	10.4
Pneumonia	11.8	8.7
Bronchitis	7.1	7.5

In general, adverse reactions reported in clinical trials of patients with cancer receiving chemotherapy were consistent with the underlying disease and the treatment with chemotherapy.

All Indications

Skin: *Rarely* (0.01–0.1%): skin reactions such as rash, pruritus, urticaria, or injection site reactions.

Other: *Very rare* (< 0.01%): anaphylactoid reactions.

In very rare cases (< 0.01%) particularly when starting treatment, flu-like symptoms such as fever, chills, headaches, pain in the limbs, malaise and/or bone pain have been reported. These reactions were mild to moderate in nature and subsided after a couple of hours or days.

Post-Marketing Experience

Epoetin beta *rch* has been marketed in Europe and other countries since 1990.

In isolated cases, neutralising anti erythropoietin antibody-mediated pure red cell aplasia (PRCA) associated with NEORECORMON therapy has been reported.

With the exception of anti erythropoietin antibody-mediated PRCA, the safety information collected during post marketing experience reflects the expected adverse event profile in these populations and the adverse drug reaction profile of epoetin beta.

DOSAGE AND ADMINISTRATION

General

Important: Use the lowest dose of NEORECORMON that will gradually increase the haemoglobin concentration. NEORECORMON dosing regimens are different for each of the indications described in this section.

It is recommended that the first dose of NEORECORMON be administered under the supervision of a healthcare professional.

Treatment of Anaemia in Patients with Chronic Kidney Disease

NEORECORMON may be administered by either intravenous or subcutaneous injection, however, subcutaneous should be considered where feasible since lower doses are required. Generally, the subcutaneous maintenance dose is approximately 20–35% lower than the intravenous maintenance dose. In the case of intravenous administration, the solution should be injected over approximately 2 minutes (e.g. in haemodialysis patients via the arteriovenous fistula at the end of dialysis). For non-haemodialysis patients, subcutaneous administration is preferred in order to avoid puncture of peripheral veins.

The recommended haemoglobin target is 100–120 g/L. The target haemoglobin should be determined individually in the presence of hypertension or existing cardiovascular,

cerebrovascular or peripheral vascular diseases. It is recommended that haemoglobin is monitored at regular intervals until stabilised and periodically thereafter (see PRECAUTIONS, Cardiovascular and Thrombotic events).

Treatment with NEORECORMON is divided into two stages:

1. Correction phase

Subcutaneous administration

The recommended starting dose is 60 IU/kg body weight/week, administered as a single weekly injection or in up to 7 divided doses. The dose may be increased every 4 weeks by 60 IU/kg body weight/week if the haemoglobin increase is not adequate (Hb < 1.5 g/L per week).

Intravenous administration

The initial dose is 120 IU/kg body weight/week, administered in 3 divided doses. The dose may be raised after 4 weeks to 240 IU/kg body weight/week. If further increments are needed they should be at 60 IU/kg body weight/week, at monthly intervals.

2. Maintenance phase

To maintain haemoglobin between 100–120 g/L the dose is initially reduced to half of the previously administered amount.

In the case of subcutaneous administration, the weekly dose can be given as a single injection or in up to 7 divided doses. Patients who are stable on a once weekly dosing regimen may be switched to once every 2 weeks administration. In this case dose increases may be necessary.

Dose adjustment

Increases in dose should not be made more frequently than once a month. The dose for each patient should be adjusted so that the haemoglobin concentration does not exceed 120 g/L. If the haemoglobin is increasing and approaching 120 g/L, the dose should be reduced by approximately 25–50%. If the haemoglobin continues to increase, the dose should be temporarily withheld until the haemoglobin begins to decrease, at which point therapy should be re-initiated at a dose approximately 25–50% below the previous dose. If the haemoglobin increases by more than 10 g/L in any 2 week period, the dose should be decreased by approximately 25–50%.

The maximum dose should not exceed 720 IU/kg body weight/week.

NEORECORMON is normally a lifelong therapy. It can however, be interrupted if necessary, at any time. Data on the once weekly dosing schedule are based on clinical studies with a treatment duration of 24 weeks.

Use in Children and Adolescents

The results of clinical studies in children and adolescents have shown that on average, the younger the patient, the higher the NEORECORMON dose required. Nevertheless, the recommended dosing schedule should be followed as the individual response cannot be predicted.

Treatment for Increasing the Amount of Autologous Blood

The dose may be administered by either intravenous or subcutaneous injection. In the case of intravenous administration, the solution should be injected over approximately 2 minutes.

The dose for autologous blood donation prior to elective surgery is 400–1600 IU/kg body weight/week i.v. or 300–1200 IU/kg body weight/week s.c. administered in 2 divided doses, for a maximum of 4 weeks.

If the patient's PCV ≥ 33 % or Hb > 110 g/L, NEORECORMON may be administered at the end of the blood donation. Patients with pre-existing cardiac diseases should be monitored carefully (see PRECAUTIONS – Cardiovascular and Thrombotic Events).

The dose must be determined for each patient as a function of the required amount of pre-donated blood and the endogenous red cell reserve.

The required amount of pre-donated blood depends on the anticipated blood loss, the physical condition of the patient and use, if any, of blood conserving procedures. This amount should be that quantity which is expected to be sufficient to avoid homologous blood transfusions. The required amount of pre-donated blood is expressed in units whereby one unit in the nomogram is equivalent to 180 ml red cells.

The ability to donate blood depends predominantly on the patient's blood volume and baseline PCV. Both variables determine the endogenous red cell reserve, which can be calculated according to the following formula:

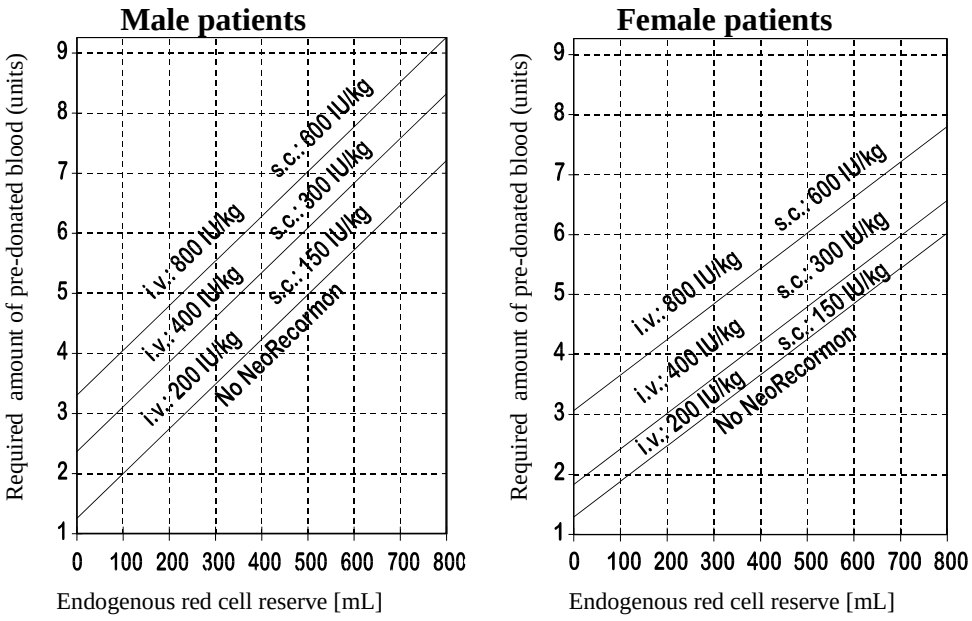
$$\text{Endogenous red cell reserve} = \frac{\text{blood volume [mL]} \times (\text{PCV} - 33)}{100}$$

male: blood volume [mL] = 44 [mL/kg] x body weight [kg] + 1600 [mL]

female: blood volume [mL] = 41 [mL/kg] x body weight [kg] + 1200 [mL]

(body weight ≥ 45 kg)

The indication for NEORECORMON treatment and, if given, the single dose should be determined from the required amount of pre-donated blood and the endogenous red cell reserves according to the following graphs.



The single dose, as determined above, is administered twice weekly over 4 weeks. The maximum dose should not exceed 1600 IU/kg body weight/week for i.v. and 1200 IU/kg body weight/week for s.c. administration.

Prevention of Anaemia of Prematurity

The solution is administered subcutaneously at a dose of 750 IU/kg body weight/week administered in 3 divided doses.

NEORECORMON treatment should be commenced as early as possible, preferably by day 3 of life. Premature infants who have already been transfused prior to NEORECORMON treatment are not likely to benefit as much as non-transfused infants. The treatment should last for 6 weeks.

Treatment of Anaemia in Patients with Non-Myeloid Malignancies

NEORECORMON treatment should not be commenced unless the haemoglobin falls below 100–110 g/L. The recommended initial dose is 450 IU/kg body weight/week, administered subcutaneously as a single weekly injection or in 3 to 7 divided doses. If after 4 weeks, a patient does not show a satisfactory response in terms of haemoglobin values, then the dose should be doubled. The therapy should be continued up to 4 weeks after the end of chemotherapy. The maximum dose should not exceed 900 IU/kg body weight/week.

If haemoglobin falls by more than 10 g/L in the next cycle of chemotherapy despite concomitant NEORECORMON therapy, further administration may not be effective.

Rapid increases in haemoglobin concentrations or the use of erythropoietin in subjects with normal haemoglobin concentrations may result in an increased risk of thrombotic adverse events (see PRECAUTIONS – Cardiovascular and Thrombotic Events). Therefore, a rise > 10 g/L per fortnight or haemoglobin concentration > 120 g/L should be avoided. If the haemoglobin concentration is rising by more than 10 g/L per fortnight, reduce the NEORECORMON dose by approximately 25%. If the haemoglobin concentration exceeds 120 g/L, discontinue NEORECORMON until it falls below 120 g/L and then restart NEORECORMON at a dose 25% below the previous dose. It is recommended that haemoglobin is monitored at regular intervals until stabilised and periodically thereafter (see PRECAUTIONS, Cardiovascular and Thrombotic Events).

Administration

Incompatibilities: In the absence of compatibility studies, NEORECORMON should not be mixed with other medicinal products.

Remove the cap from the syringe and affix the needle provided. Only solutions which are clear or slightly opalescent, colourless and practically free of visible particles should be injected. NEORECORMON pre-filled syringes are sterile but do not contain preservatives. Product is for single use in one patient only.

OVERDOSAGE

The therapeutic margin of NEORECORMON is very wide. Even at very high serum levels, no symptoms of poisoning have been observed.

Overdose can result in manifestations of an exaggerated pharmacodynamic effect e.g. excessive erythropoiesis, which may be associated with life-threatening complications to the cardiovascular system. In cases of excessive haemoglobin levels, NEORECORMON should be temporarily withheld (see DOSAGE and ADMINISTRATION). If clinically indicated, phlebotomy may be performed.

PRESENTATION AND STORAGE CONDITIONS

NEORECORMON is available as pre-filled syringes in the following strengths:

- 2,000 IU/0.3 mL [6 per pack],
- 3,000 IU/0.3 mL [6 per pack],
- 4,000 IU/0.3 mL [6 per pack],
- 5,000 IU/0.3 mL [6 per pack],
- 6,000 IU/0.3 mL [6 per pack],
- 10,000 IU/0.6 mL [6 per pack]

Storage Conditions

NEORECORMON must not be used after the expiry date.

Store continuously in the refrigerator at 2°C to 8°C. Do not freeze. Protect from light.

The pre-filled syringes are for single use in one patient only. Discard any residue. For ambulatory use, the product may be removed from refrigerated storage (2°C to 8°C) for one single period of up to a maximum of 3 days at room temperature (up to 25 °C).

Disposal of Medicines

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

Disposal of syringes/sharps

The following points should be strictly adhered to regarding the use and disposal of the pre-filled syringe and medicinal sharps:

- Needles and syringes should never be reused.
- Place all used needles and syringes into a sharps container (puncture-proof disposable container).
- Keep this container out of the reach of children.
- Avoid placing used sharps containers in the household waste.
- Dispose of the full container according to local requirements or as instructed by your healthcare provider.

NAME AND ADDRESS OF SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4. Prescription only medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

9 January 2006

DATE OF MOST RECENT AMENDMENT

10 July 2013