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RECORMON®

Epoetin beta

PRE-FILLED SYRINGE FOR SUBCUTANEOUS OR INTRAVENOUS INJECTION

1. NAME OF THE MEDICINAL PRODUCT

RECORMON® 4000 IU solution for injection in Pre-filled Syringe
RECORMON® 5000 IU solution for injection in Pre-filled Syringe
RECORMON® 6000 IU solution for injection in Pre-filled Syringe
RECORMON® 10,000 IU solution for injection in Pre-filled Syringe
RECORMON® 30,000 IU solution for injection in Pre-filled Syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Recormon 4000 IU solution for injection in pre-filled syringe
One pre-filled syringe with 0.3 ml solution for injection contains 4000 international units (IU) corresponding to 33.2 micrograms epoetin beta)/, * (recombinant human erythropoietin).
One ml solution for injection contains 13,333 IU epoetin beta.

Recormon 5000 IU solution for injection in pre-filled syringe
One pre-filled syringe with 0.3 ml solution for injection contains 5000 international units (IU) corresponding to 41.5 micrograms epoetin beta/ * (recombinant human erythropoietin).
One ml solution for injection contains 16,667 IU epoetin beta

Recormon 6000 IU solution for injection in pre-filled syringe
One pre-filled syringe with 0.3 ml solution for injection contains 6000 international units (IU) corresponding to 49.8 micrograms epoetin beta, * (recombinant human erythropoietin). One ml solution for injection contains 20,000 IU epoetin beta.

Recormon 10,000 IU solution for injection in pre-filled syringe
One pre-filled syringe with 0.6 ml solution for injection contains 10,000 international units (IU) corresponding to 83 micrograms epoetin beta * (recombinant human erythropoietin). One ml solution for injection contains 16,667 IU epoetin beta.

Recormon 30,000 IU solution for injection in pre-filled syringe
One pre-filled syringe with 0.6 ml solution for injection contains 30,000 international units (IU) corresponding to 250 micrograms epoetin beta* (recombinant human erythropoietin).
One ml solution for injection contains 50,000 IU epoetin beta.

*produced in Chinese Hamster Ovary cells (CHO) by recombinant DNA technology.

Excipient(s) with known effect:

Phenylalanine (up to 0.3 mg/syringe)
Sodium (less than 1 mmol/syringe)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Colourless, clear to slightly opalescent solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Recormon is indicated for:

- Treatment of anaemia associated with chronic renal failure (renal anaemia) in patients on dialysis.
- Treatment of symptomatic renal anaemia in patients not yet undergoing dialysis.
- Treatment of anaemia in adult patients with solid tumors receiving chemotherapy.
- Treatment of anaemia in adult patients with multiple myeloma, low grade non-Hodgkin's lymphoma or chronic lymphocytic leukemia, who have a relative erythropoietin deficiency and are receiving anti-tumor therapy. Deficiency is defined as an inappropriately low serum erythropoietin level in relation to the degree of anaemia.
- Increasing the yield of autologous blood from patients in a pre-donation program. Its use in this indication must be balanced against the reported increased risk of thromboembolic events. Treatment should only be given to patients with moderate anaemia (Hb 10-13 g/dL [6.21-8.07 mmol/L], no iron deficiency) if blood conserving procedures are not available or insufficient when the scheduled major elective surgery requires a large volume of blood (4 or more units of blood for females or 5 or more units for males).

4.2 Posology and method of administration

Therapy with Recormon should be initiated by physicians experienced in the above mentioned indications. As anaphylactoid reactions were observed in isolated cases, it is recommended that the first dose be administered under medical supervision.

Posology

Treatment of anemic patients with chronic renal failure

In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL. No trial has identified a hemoglobin target level, RECORMON dose, or dosing strategy that does not increase these risks. Individualize dosing and use the lowest dose of RECORMON sufficient to reduce the need for RBC transfusions [see Warnings and Precautions].

Physicians and patients should weigh the possible benefits of decreasing transfusions against the increased risks of death and other serious cardiovascular adverse events.

Anemia symptoms and sequelae may vary with age, gender, and overall burden of disease; a physician's evaluation of the individual patient's clinical course and condition is necessary. Recormon should be administered either subcutaneously or intravenously in order to increase haemoglobin to not greater than 11 g/dl. Subcutaneous use is preferable in patients who are not receiving haemodialysis to avoid puncture of peripheral veins. In case of intravenous administration, the solution should be injected over approx. 2 minutes, e.g. in haemodialysis patients via the arterio-venous fistula at the end of dialysis.

For patients with Chronic Renal Failure on dialysis:

- Initiate RECORMON treatment when the hemoglobin level is less than 10 g/dL.
- If the hemoglobin level approaches or exceeds 11 g/dL, reduce or interrupt the dose of RECORMON

For patients with Chronic Renal Failure not on dialysis:

Consider initiating RECORMON treatment only when the hemoglobin level is less than 10 g/dL and the following considerations apply:

- The rate of hemoglobin decline indicates the likelihood of requiring a RBC transfusion and, reducing the risk of alloimmunization and/or other RBC transfusion-related risks is a goal.

- If the hemoglobin level exceeds 10 g/dL, reduce or interrupt the dose of RECORMON, and use the lowest dose of RECORMON sufficient to reduce the need for RBC transfusions.

Due to intra-patient variability, occasional individual haemoglobin values for a patient above and below the desired haemoglobin level may be observed. Haemoglobin variability should be addressed through dose management, with consideration for the haemoglobin target range of 10 g/dl (6.2 mmol/l) to 11 g/dl (6.83 mmol/l). A sustained haemoglobin level of greater than 11 g/dl should be avoided; guidance for appropriate dose adjustment for when haemoglobin values exceeding 11 g/dl are observed are described below.

A rise in haemoglobin of greater than 2 g/dl (1.25 mmol/l) over a four week period should be avoided. If it occurs, appropriate dose adjustment should be made as provided. If the rate of rise in haemoglobin is greater than 2 g/dl (1.25 mmol/l) in one month or if the haemoglobin level is increasing and approaching 11 g/dl the dose is to be reduced by approximately 25 %. If the haemoglobin level continues to increase, therapy should be interrupted until the hemoglobin level begins to decrease, at which point therapy should be restarted at a dose approximately 25 % below the previously administered dose.

Patients should be monitored closely to ensure that the lowest approved effective dose of Recormon is used to provide adequate control of the symptoms of anemia whilst maintaining a haemoglobin concentration below or at 11 g/dl.

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

In the presence of hypertension or existing cardiovascular, cerebrovascular or peripheral vascular diseases, the weekly increase in Hb and the target Hb should be determined individually taking into account the clinical picture.

Treatment with Recormon is divided into two stages.

1. <u>Correction phase</u>
- Subcutaneous administration:
  The initial dosage is 3 x 20 IU/kg body weight per week. The dosage may be increased every 4 weeks by 3 x 20 IU/kg and week if the increase of Hb is not adequate (< 0.25 g/dl per week).
  The weekly dose can also be divided into daily doses.
- Intravenous administration:
  The initial dosage is 3 x 40 IU/kg per week. The dosage may be raised after 4 weeks to 80 IU/kg - three times per week - and by further increments of 20 IU/kg if needed, three times per week, at monthly intervals.

For both routes of administration, the maximum dose should not exceed 720 IU/kg per week.

2. <u>Maintenance phase</u>

To maintain an Hb of between 10 and 11 g/dl, the dosage is initially reduced to half of the previously administered amount. Subsequently, the dose is adjusted at intervals of one or two weeks individually for the patient (maintenance dose).

In the case of subcutaneous administration, the weekly dose can be given as one injection per week or in divided doses three or seven times per week. Patients who are stable on a once weekly dosing regimen may be switched to once every two weeks administration. In this case dose increases may be necessary.

Results of clinical studies in children have shown that, on average, the younger the patients, the higher the Recormon doses required. Nevertheless, the recommended dosing schedule should be followed as the individual response cannot be predicted.

Treatment with Recormon is normally a long-term 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.

Treatment of chemotherapy-induced anemia in cancer patients:

Recormon should be administered by the subcutaneous route to patients with anemia (e.g. haemoglobin concentration ≤ 10g/dl (6.2 mmol/l)). Anemia symptoms and sequelae may vary with age, gender, and overall burden of disease; a physician's evaluation of the individual patient's clinical course and condition is necessary.

The weekly dose can be given as one injection per week or in divided doses 3 to 7 times per week.

The recommended initial dose is 30,000 IU per week (corresponding to approximately 450 IU/kg body weight per week, based on an average weighted patient).

Due to intra-patient variability, occasional individual haemoglobin values for a patient above and below the desired haemoglobin level may be observed. Haemoglobin variability should be addressed through dose management, with consideration for the haemoglobin target range of 10 g/dl (6.2 mmol/l) to 11 g/dl (6.83 mmol/l). A sustained haemoglobin level of greater than 11 g/dl should be avoided; guidance for appropriate dose adjustment for when haemoglobin values exceeding 11 g/dl are observed are described below.

If, after 4 weeks of therapy, the haemoglobin value has increased by at least 1 g/dl (0.62 mmol/l), the current dose should be continued. If the haemoglobin value has not increased by at least 1 g/dl (0.62 mmol/l), a doubling of the weekly dose should be considered. If, after 8 weeks of therapy, the haemoglobin value has not increased by at least 1 g/dl (0.62 mmol/l), response is unlikely and treatment should be discontinued.
The therapy should be continued up to 4 weeks after the end of chemotherapy.

The maximum dose should not exceed 60,000 IU per week.

Once the therapeutic objective for an individual patient has been achieved, the dose should be reduced by 25 to 50 % in order to maintain haemoglobin at that level. Appropriate dose titration should be considered.

If the haemoglobin exceeds 11 g/dl the dose should be reduced by approximately 25 to 50 %. Treatment with Recormon should be temporarily discontinued if haemoglobin levels exceed 13 g/dl (8.1 mmol/l). Therapy should be reinitiated at approximately 25 % lower than the previous dose after haemoglobin levels fall to 11 g/dl or below.

If the rise in haemoglobin is greater than 2 g/dl (1.3 mmol/l) in 4 weeks, the dose should be reduced by 25 to 50 %.

Patients should be monitored closely to ensure that the lowest approved dose of Recormon is used to provide adequate control of the symptoms of anemia.

Treatment for increasing the amount of autologous blood:
The solution is administered intravenously over approx. 2 minutes or subcutaneously.
Recormon is administered twice weekly over 4 weeks. On those occasions where the patient's PCV allows blood donation, i.e. PCV ≥ 33 %, Recormon is administered at the end of blood donation.
During the entire treatment period, a PCV of 48 % should not be exceeded.

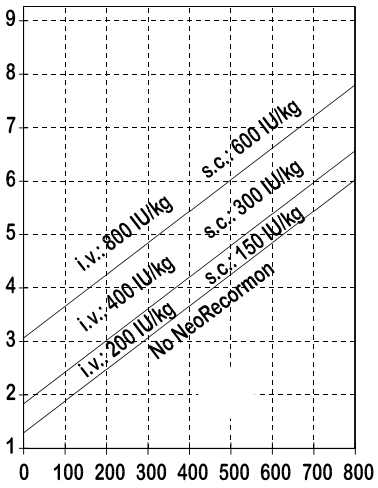
The dosage must be determined by the surgical team individually for each patient as a function of the required amount of pre-donated blood and the endogenous red cell reserve:

1. The required amount of pre-donated blood depends on the anticipated blood loss, use of blood conserving procedures and the physical condition of the patient.
   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.
2. 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.

   Endogenous red cell reserve = blood volume [ml] x (PCV - 33) ÷ 100
   Women: blood volume [ml] = 41 [ml/kg] x body weight [kg] + 1200 [ml]
   Men: blood volume [ml] = 44 [ml/kg] x body weight [kg] + 1600 [ml]
   (body weight ≥ 45 kg)

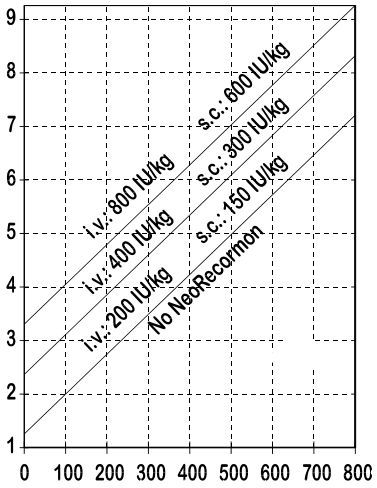
The indication for treatment with Recormon and, if given, the single dose should be determined from the required amount of pre-donated blood and the endogenous red cell reserve according to the following graphs.

Female patients
Required amount of pre-donated blood [units]



Endogenous red cell reserve [ml]

Male patients
Required amount of pre-donated blood [units]



Endogenous red cell reserve [ml]

The single dose thus determined is administered twice weekly over 4 weeks. The maximum dose should not exceed 1600 IU/kg body weight per week for intravenous or 1200 IU/kg per week for subcutaneous administration.

Method of administration

The Recormon pre-filled syringe is ready for use. Only solutions which are clear or slightly opalescent, colourless and practically free of visible particles may be injected.

Recormon in pre-filled syringe is a sterile but unpreserved product. Under no circumstances should more than one dose be administered per syringe; the medicinal product is for single use only.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients listed in section 6.1.

Poorly controlled hypertension.

In the indication "increasing the yield of autologous blood": myocardial infarction or stroke in the month preceding treatment, unstable angina pectoris, increased risk of deep venous thrombosis such as history of venous thromboembolic disease.

4.4 Special warnings and precautions for use

Recormon should be used with caution in the presence of refractory anemia with excess blasts in transformation, epilepsy, thrombocytosis, and chronic liver failure. Folic acid and vitamin B_{12} deficiencies should be ruled out as they reduce the effectiveness of Recormon.

Caution should be exercised with escalation of Recormon doses in patients with chronic renal failure since high cumulative epoetin doses may be associated with an increased risk of mortality, serious cardiovascular and cerebrovascular events. In patients with a poor haemoglobin response to epoetins, alternative explanations for the poor response should be considered (see sections 4.2 and 5.1).

In order to ensure effective erythropoiesis, iron status should be evaluated for all patients prior to and during treatment and supplementary iron therapy may be necessary and conducted in accordance with therapeutic guidelines.

Severe aluminium overload due to treatment of renal failure may compromise the effectiveness of Recormon.

The indication for treatment with Recormon 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.

Pure red cell aplasia (PRCA)

PRCA caused by neutralising anti-erythropoietin antibodies has been reported in association with erythropoietin therapy, including Recormon. 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 Recormon (see section 4.8).

PRCA in patients with Hepatitis C
A paradoxical decrease in haemoglobin and development of severe anemia associated with low reticulocyte counts should prompt to discontinue treatment with epoetin and perform anti-erythropoietin antibody testing. Cases have been reported in patients with hepatitis C treated with interferon and ribavirin, when epoetins are used concomitantly. Epoetins are not approved in the management of anemia associated with hepatitis C.

Blood pressure monitoring
An increase in blood pressure or aggravation of existing hypertension, especially in cases of rapid PCV increase can occur. These increases in blood pressure can be treated with medicinal products. If blood pressure rises cannot be controlled by drug therapy, a transient interruption of Recormon therapy is recommended. Particularly at beginning of therapy, regular monitoring of the blood pressure is recommended, including between dialyses. Hypertensive crisis with encephalopathy-like symptoms may occur and 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.

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported in association with epoetin treatment (see section 4.8). More severe cases have been observed with long-acting epoetins. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, Recormon should be withdrawn immediately and an alternative treatment considered.If the patient has developed a severe cutaneous skin reaction such as SJS or TEN due to the use of Recormon, treatment with ESA must not be restarted in this patient at any time.

Chronic renal failure
In chronic renal failure patients there may be a moderate dose-dependent rise in the platelet count within the normal range during treatment with Recormon, especially after intravenous administration. This regresses during the course of continued therapy. It is recommended that the platelet count be monitored regularly during the first 8 weeks of therapy.

Haemoglobin concentration
In patients with chronic renal failure, maintenance haemoglobin concentration should not exceed the upper limit of the target haemoglobin concentration recommended in section 4.2. In clinical trials, an increased risk of death and serious cardiovascular events or cerebrovascular events including stroke was observed when erythropoiesis stimulating agents (ESAs) were administered to target a haemoglobin of greater than 11 g/dl.

No trial has identified a hemoglobin target level, epoetin dose, or dosing strategy that does not Increase these risks.

Controlled clinical trials have not shown significant benefits attributable to the administration of epoetins when haemoglobin concentration is increased beyond the level necessary to control symptoms of anemia and to avoid blood transfusion.

Effect on tumour growth
Epoetins are growth factors that primarily stimulate red blood cell production. Erythropoietin receptors may be expressed on the surface of a variety of tumour cells. As with all growth factors, there is a concern that epoetins could stimulate the growth of tumours. In several controlled studies, epoetins have not been shown to improve overall survival or decrease the risk of tumour progression in patients with anemia associated with cancer.
In controlled clinical studies, use of Recormon and other erythropoiesis-stimulating agents (ESAs) have shown:
- shortened time to tumour progression in patients with advanced head and neck cancer receiving radiation therapy when administered to target a haemoglobin of greater than 14 g/dl (8.7 mmol/l),
- shortened overall survival and increased deaths attributed to disease progression at 4 months in patients with metastatic breast cancer receiving chemotherapy when administered to target a haemoglobin of 12-14 g/dl (7.5-8.7 mmol/l),
- increased risk of death when administered to target a haemoglobin of 12 g/dl (7.5 mmol/l) in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESAs are not indicated for use in this patient population.

In view of the above, in some clinical situations blood transfusion should be the preferred treatment for the management of anemia in patients with cancer. The decision to administer recombinant erythropoietins should be based on a benefit-risk assessment with the participation of the individual patient, which should take into account the specific clinical context. Factors that should be considered in this assessment should include the type of tumour and its stage; the degree of anemia; life-expectancy; the environment in which the patient is being treated; and patient preference (see section 5.1)

There may be an increase in blood pressure which can be treated with drugs. It is therefore recommended to monitor blood pressure, in particular in the initial treatment phase in cancer patients.

Platelet counts and haemoglobin level should also be monitored at regular intervals in cancer patients.

In patients in an *autologous blood predonation programme* there may be an increase in platelet count, mostly within the normal range. Therefore, it is recommended that the platelet count be determined at least once a week in these patients. If there is an increase in platelets of more than 150 x 10^9/l or if platelets rise above the normal range, treatment with Recormon should be discontinued.

In *chronic renal failure* patients an increase in heparin dose during haemodialysis is frequently required during the course of therapy with Recormon as a result of the increased packed cell volume. Occlusion of the dialysis system is possible if heparinisation is not optimum.

Early shunt revision and thrombosis prophylaxis by administration of acetylsalicylic acid, for example, should be considered in chronic renal failure patients at risk of shunt thrombosis.

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

For use of Recormon in an autologous predonation programme, the official guidelines on principles of blood donation must be considered, in particular:
- Only patients with a PCV ≥ 33 % (haemoglobin ≥ 11 g/dl [6.83 mmol/l]) should donate;
- Special care should be taken with patients below 50 kg weight;
- The single volume drawn should not exceed approx. 12 % of the patient's estimated blood volume.

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.

Misuse
Misuse by healthy persons may lead to an excessive increase in packed cell volume. This may be associated with life-threatening complications of the cardiovascular system.

Excipients
Recormon in pre-filled syringe contains up to 0.3 mg phenylalanine/syringe as an excipient. Therefore this should be taken into consideration in patients affected with severe forms of phenylketonuria.

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

Traceability of Recormon
In order to improve the traceability of erythropoiesis-stimulating agents (ESAs), the trade name of the administered ESA should be clearly recorded (or: stated) in the patient file.

4.5 Interaction with other medicinal products and other forms of interaction

The clinical results obtained so far do not indicate any interaction of Recormon with other medicinal products.
Animal experiments revealed that epoetin beta does not increase the myelotoxicity of cytostatic medicinal products like etoposide, cisplatin, cyclophosphamide, and fluorouracil.

4.6 Fertility, pregnancy and lactation

Fertility
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

Pregnancy
For epoetin beta no clinical data on exposed pregnancies are available.
Caution should be exercised when prescribing to pregnant women.

Breast-feeding
It is unknown whether epoetin beta is excreted in human milk.
A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with epoetin beta should be made taking into account the benefit of breast-feeding to the child and the benefit of epoetin beta therapy to the woman.

4.7 Effects on ability to drive and use machines

Recormon has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Based on results from clinical trials including 1725 patients approximately 8 % of patients treated with Recormon are expected to experience adverse reactions.

Anaemic patients with chronic renal failure
The most frequent adverse reaction during treatment with Recormon is an increase in blood pressure or aggravation of existing hypertension, especially in cases of rapid PCV increase (see section 4.4). 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) may also occur in individual patients with otherwise normal or low blood pressure (see section 4.4).

Shunt thromboses may occur, especially in patients who have a tendency to hypotension or whose arteriovenous fistulae exhibit complications (e.g. stenoses, aneurisms), see section 4.4. In most cases, a fall in serum ferritin values simultaneous with a rise in packed cell volume is observed (see section 4.4). In addition, transient increases in serum potassium and phosphate levels have been observed in isolated cases (see section 4.4).

In isolated cases, neutralising anti erythropoietin antibody-mediated pure red cell aplasia (PRCA) associated with Recormon therapy has been reported. In case anti-erythropoietin antibody-mediated PRCA is diagnosed, therapy with Recormon must be discontinued and patients should not be switched to another erythropoietic protein (see section 4.4).

Adverse reactions are listed in Table 1 below.

Patients with cancer
Epoetin beta treatment-related headache and hypertension which can be treated with drugs are common (see section 4.4).

In some patients, a fall in serum iron parameters is observed (see section 4.4).

Clinical studies have shown a higher frequency of thromboembolic events in cancer patients treated with Recormon compared to untreated controls or placebo. In patients treated with Recormon, this incidence is 7 % compared to 4 % in controls; this is not associated with any increase in thromboembolic mortality compared with controls.

Adverse reactions are listed in Table 2 below.

Patients in an autologous blood predonation programme

Patients in an autologous blood predonation programme have been reported to show a slightly higher frequency of thromboembolic events. However, a causal relationship with treatment with Recormon could not be established.

In placebo controlled trials temporary iron deficiency was more pronounced in patients treated with Recormon than in controls (see section 4.4).

Adverse reactions are listed in Table 3 below.

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported in association with epoetin treatment (see section 4.4)

Tabulated list of adverse reactions
Adverse reactions are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention:
very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 1: Adverse reactions attributed to the treatment with Recormon in controlled clinical trials in CKD patients

System organ class	Adverse reaction	Frequency
Vascular disorders	Hypertension Hypertensive crisis	Common Uncommon
Nervous system disorders	Headache	Common
Blood and the lymphatic system disorders	Shunt thrombosis Thrombocytosis	Rare Very rare

Table 2: Adverse reactions attributed to the treatment with Recormon in controlled clinical trials in cancer patients

System organ class	Adverse reaction	Frequency
Vascular disorders	Hypertension	Common
Blood and the lymphatic system disorders	Thromboembolic event	Common
Nervous system disorders	Headache	Common

Table 3: Adverse reactions attributed to the treatment with Recormon in controlled clinical trials in patients in an autologous blood predonation programme

System organ class	Adverse reaction	Frequency
Nervous system disorders	Headache	Common

Description of selected adverse reactions

Rarely epoetin beta treatment-related skin reactions such as rash, pruritus, urticaria or injection site reactions may occur. In very rare cases epoetin beta treatment-related anaphylactoid reactions have been reported. However, in controlled clinical studies no increased incidence of hypersensitivity reactions was found.

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

Data from a controlled clinical trial with epoetin alfa or darbepoetin alfa, reported an incidence of stroke as common.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antianemic, ATC code: B03XA01

Mechanism of action

Erythropoietin is a glycoprotein that stimulates the formation of erythrocytes from its committed progenitors. It acts as a mitosis stimulating factor and differentiation hormone.

Epoetin beta, the active substance of Recormon is identical in its amino acid and carbohydrate composition to erythropoietin that has been isolated from the urine of anaemic patients.

The biological efficacy of epoetin beta has been demonstrated after intravenous and subcutaneous administration in various animal models *in vivo* (normal and uraemic rats, polycythaemic mice, dogs). After administration of

epoetin beta, the number of erythrocytes, the Hb values and reticulocyte counts increase as well as the ^{59}Fe-incorporation rate.

An increased ^{3}H-thymidine incorporation in the erythroid nucleated spleen cells has been found *in vitro* (mouse spleen cell culture) after incubation with epoetin beta.
Investigations in cell cultures of human bone marrow cells showed that epoetin beta stimulates erythropoiesis specifically and does not affect leucopoiesis. Cytotoxic actions of epoetin beta on bone marrow or on human skin cells were not detected.

After single dose administration of epoetin beta no effects on behaviour or locomotor activity of mice and circulatory or respiratory function of dogs were observed.

Clinical efficacy and safety

In a randomised, double-blind, placebo-controlled study of 4,038 chronic renal failure patients not on dialysis with type 2 diabetes and haemoglobin levels ≤ 11 g/dL, patients received either treatment with darbepoetin alfa to target haemoglobin levels of 13 g/dL or placebo (see section 4.4). The study did not meet either primary objective of demonstrating a reduction in risk for all-cause mortality, cardiovascular morbidity, or end stage renal disease (ESRD). Analysis of the individual components of the composite endpoints showed the following HR (95% CI): death 1.05 (0.92, 1.21), stroke 1.92 (1.38, 2.68), congestive heart failure (CHF) 0.89 (0.74, 1.08), myocardial infarction (MI) 0.96 (0.75, 1.23), hospitalisation for myocardial ischaemia 0.84 (0.55, 1.27), ESRD 1.02 (0.87, 1.18).

Pooled post-hoc analyses of clinical studies with ESAs have been performed in CRF patients (on dialysis, not on dialysis, with or without diabetes). A tendency towards increased risk estimates for all-cause mortality, cardiovascular and cerebrovascular events associated with higher cumulative ESA doses independent of the diabetes or dialysis status was observed (see sections 4.2 and 4.4).

Erythropoietin is a growth factor that primarily stimulates red cell production. Erythropoietin receptors may be expressed on the surface of a variety of tumour cells.

Survival and tumour progression have been examined in five large controlled studies involving a total of 2833 patients, of which four were double-blind placebo-controlled studies and one was an open-label study. Two of the studies recruited patients who were being treated with chemotherapy. The target haemoglobin concentration in two studies was >13 g/dl; in the remaining three studies it was 12-14 g/dl. In the open-label study there was no difference in overall survival between patients treated with recombinant human erythropoietin and controls. In the four placebo-controlled studies the hazard ratios for overall survival ranged between 1.25 and 2.47 in favour of controls. These studies have shown a consistent unexplained statistically significant excess mortality in patients who have anemia associated with various common cancers who received recombinant human erythropoietin compared to controls. Overall survival outcome in the trials could not be satisfactorily explained by differences in the incidence of thrombosis and related complications between those given recombinant human erythropoietin and those in the control group.

An individual patient data based meta-analysis, which included data from all 12 controlled clinical studies in anaemic cancer patients conducted with Recormon (n=2301), showed an overall hazard ratio point estimate for survival of 1.13 in favour of controls (95 % CI 0.87, 1.46). In patients with baseline haemoglobin ≤ 10 g/dl (n=899), the hazard ratio point estimate for survival was 0.98 (95 % CI 0.68 to 1.40). An increased relative risk for thromboembolic events was observed in the overall population (RR 1.62, 95 % CI: 1.13, 2.31).

A patient-level data analysis has also been performed on more than 13,900 cancer patients (chemo-, radio-, chemoradio- or no therapy) participating in 53 controlled clinical trials involving several epoetins. Meta-analysis of overall survival data produced a hazard ratio point estimate of 1.06 in favour of controls (95% CI: 1.00, 1.12; 53 trials and 13,933 patients) and for cancer patients receiving chemotherapy, the overall survival hazard ratio was 1.04 (95% CI: 0.97, 1.11; 38 trials and 10, 441 patients). Meta-analyses also indicate consistently a significantly increased relative risk of thromboembolic events in cancer patients receiving recombinant human erythropoietin (see section 4.4).

In very rare cases, neutralising anti-erythropoietin antibodies with or without pure red cell aplasia (PRCA) occurred during rHuEPO therapy.

Premature infants
In premature infants there may be a slight rise in platelet counts, particularly up to day 12 - 14 of life, therefore platelets should be monitored regularly.

In *preterm infants* a potential risk of erythropoietin to cause retinopathy could not be excluded, therefore caution should be exercised and the decision to treat a preterm infant should be balanced against the potential benefit and risk of this treatment and available alternative options.

In premature infants, a fall in serum ferritin values is very common.

5.2 Pharmacokinetic properties

Pharmacokinetic investigations in healthy volunteers and uraemic patients show that the half-life of intravenously administered epoetin beta is between 4 and 12 hours and that the distribution volume corresponds to one to two times the plasma volume. Analogous results have been found in animal experiments in uraemic and normal rats.

After subcutaneous administration of epoetin beta to uraemic patients, the protracted absorption results in a serum concentration plateau, whereby the maximum concentration is reached after an average of 12 - 28 hours. The terminal half-life is higher than after intravenous administration, with an average of 13 - 28 hours.

Bioavailability of epoetin beta after subcutaneous administration is between 23 and 42 % as compared with intravenous administration.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and toxicity to reproduction.
A carcinogenicity study with homologous erythropoietin in mice did not reveal any signs of proliferative or tumourigenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections.
Glycine,
Disodium hydrogen phosphate,
L-Leucine,
L-Isoleucine,
Calcium chloride,
Sodium dihydrogen phosphate,
Sodium chloride,
L-Threonine,
L-Glutamic acid,
L-Phenylalanine,
Polysorbate 20,
Urea

6.2 Incompatibilities

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

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

Keep the pre-filled syringe in the outer carton, in order to protect from light.

For the purpose of ambulatory use, the patient may remove the medicinal product from the refrigerator and store it at room temperature (not above 25°C) for one single period of up to 3 days.

6.5 Nature and contents of container

Pre-filled syringe (Type I glass) with a tip cap and a plunger stopper (bromobutyl rubber) with an injection needle (27G1/2).

- *Recormon, 4000 IU/0.3 mL, 5000 IU/0.3 mL, 6000 IU/0.3 mL, 10, 000 IU/0.6 mL Pre-filled Syringes:*
  Pack sizes of 6 pre-filled syringes and 6 needles.
- *Recormon 30,000 IU / 0.6 mL Pre-filled syringe:* Pack size of 4 pre-filled syringes and 4 needles.
  Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

First wash your hands!

1. Remove one syringe from the pack and check that the solution is clear, colourless and practically free from visible particles. Remove the cap from the syringe.
2. Remove one needle from the pack, fix it on the syringe and remove the protective cap from the needle.
3. Expel air from the syringe and needle by holding the syringe vertically and gently pressing the plunger upwards. Keep pressing the plunger until the amount of Recormon in the syringe is as prescribed.
4. Clean the skin at the site of injection using an alcohol wipe. Form a skin fold by pinching the skin between thumb and forefinger. Hold the syringe barrel near to the needle, and insert the needle into the skin fold with a quick, firm action. Inject the Recormon solution. Withdraw the needle quickly and apply pressure over the injection site with a dry, sterile pad.

This medicinal product is for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

7. LICENSE HOLDER

Roche Pharmaceuticals (Israel) Ltd., P.O. B. 6391, Hod Hasharon 4524079.

8. LICENSE NUMBERS

Recormon 4000 IU Pre-filled Syringe: 121 08 30142 00
Recormon 5000 IU Pre-filled Syringe: 114 42 29586 00
Recormon 6000 IU Pre-filled Syringe: 121 40 30195 00
Recormon 10, 000 IU Pre-filled Syringe: 114 43 29587 00
Recormon 30, 000 IU pre-filled Syringe: 132 41 31158 00

9. MANUFACTURER

Roche Diagnostics GmbH ,Germany - Sandhofer strasse 116, Mannheim,Germany

Medicine: keep out of reach of children