Recormon®

Epoetin beta

10114507 FE

1. DESCRIPTION

1.1 Therapeutic / Pharmacologic Class of Drug

Antianemic agent

ATC code: B03XA

1.2 Type of Dosage Form

Powder and solvent for solution for injection (multidose and cartridges).

Solution for injection (pre-filled syringes).

1.3 Route of Administration

Solution for intravenous (i.v.) or subcutaneous (s.c.) injection.

1.4 Qualitative and Quantitative Composition

Active ingredient: epoetin beta (recombinant human erythropoietin: produced by recombinant DNA technology in CHO cell line).

Recormon is provided as lyophilisate and solvent for solution for injection, as lyophilisate and solvent for solution for injection in cartridge, and as solution for injection in pre-filled syringes.

The reconstituted product is a colorless, clear to slightly opalescent solution.

Lyophilisate and solvent for solution for injection:
50,000 IU = 415 micrograms epoetin beta / vial + 10 ml solvent (water for injections with benzyl alcohol and benzalkonium chloride as preservatives) / ampoule
100,000 IU = 830 micrograms epoetin beta / vial + 5 ml solvent (water for injections with benzyl alcohol and benzalkonium chloride as preservatives) / ampoule

Lyophilisate and solvent for solution for injection in cartridge:
10,000 IU = 83 micrograms epoetin beta + 1 ml solvent (water for injections with benzyl alcohol and benzalkonium chloride as preservatives)
20,000 IU = 166 micrograms epoetin beta + 1 ml solvent (water for injections with benzyl alcohol and benzalkonium chloride as preservatives)
60,000 IU = 498 micrograms epoetin beta + 1 ml solvent (water for injections with benzyl alcohol and benzalkonium chloride as preservatives)

Solution for injection in pre-filled syringe:
500 IU = 4.15 micrograms epoetin beta with 0.3 ml solution for injection
1000 IU = 8.3 micrograms epoetin beta with 0.3 ml solution for injection
2000 IU = 16.6 micrograms epoetin beta with 0.3 ml solution for injection
3000 IU = 24.9 micrograms epoetin beta with 0.3 ml solution for injection
4000 IU = 33.2 micrograms epoetin beta with 0.3 ml solution for injection
5000 IU = 41.5 micrograms epoetin beta with 0.3 ml solution for injection
6000 IU = 49.8 micrograms epoetin beta with 0.3 ml solution for injection
10,000 IU = 83 micrograms epoetin beta with 0.6 ml solution for injection
20,000 IU = 166 micrograms epoetin beta with 0.6 ml solution for injection
30,000 IU = 250 micrograms epoetin beta with 0.6 ml solution for injection

List of excipients:
All presentations contain phenylalanine (up to 5.0 mg per multidose vial, up to 0.5 mg per cartridge, up to 0.3 mg per pre-filled syringe) (see section 2.4.1 General, Warnings and Precautions).

The solvent used for vials and cartridges contains benzyl alcohol (up to 40 mg per multidose solvent ampoule, up to 4 mg per cartridge) (see section 2.3 Contraindications).

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)
- Treatment of symptomatic anemia associated with chronic kidney disease (CKD) in patients on dialysis.
- Treatment of symptomatic renal anemia in patients not yet undergoing dialysis.
- Prevention of anemia of prematurity in infants with a birth weight of 750 to 1500 g and a gestational age of less than 34 weeks.
- Treatment of symptomatic anemia in adult patients with non-myeloid malignancies receiving chemotherapy.
- 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 anemia (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).

2.2 Dosage and 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.

Lyophilisate and solvent for solution for injection:
The multidose preparation can be used for several patients. To avoid the risk of cross-infection always follow aseptic techniques and use disposable sterile syringes and needles for each administration.

Lyophilisate and solvent for solution for injection in cartridge:
Recormon in cartridge should only be used with the Reco-Pen.

Solution for injection in pre-filled syringe:
The Recormon pre-filled syringe is ready for use. Under no circumstances should more than one dose be administered per syringe; the medicinal product is for single use only.

Treatment of patients with anemia due to chronic kidney disease
The reconstituted solution can be administered subcutaneously or intravenously. In case of intravenous administration, the solution should be injected over approx. 2 minutes, e.g. in hemodialysis patients via the arterio-venous fistula at the end of dialysis.

For non-hemodialysed patients, subcutaneous administration should always be preferred in order to avoid puncture of peripheral veins.

In CKD patients, the aim of treatment is to reach a target Hb level of 10-12 g/dl. An Hb level of 12 g/dl should not be exceeded. If the rise in hemoglobin is greater than 2 g/dl (1.3 mmol/l) in 4 weeks, an appropriate dose reduction should be considered. 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. Patients should be monitored closely to ensure that the lowest dose of Recormon is used to provide adequate control of the symptoms of anemia.

Treatment with Recormon is divided into two stages.

1. Correction phase
- *Subcutaneous administration (all dosage forms):*
  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 per 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.

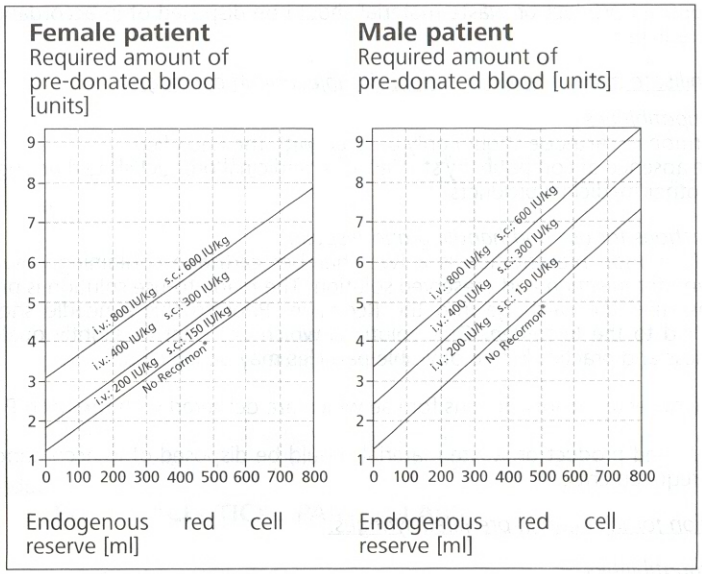
- *Intravenous administration (powder and solvent for solution for injection and pre-filled syringes only):*
  The initial dosage is 3 x 40 IU/kg per week. The dosage may be raised after 4 weeks to 80 IU/kg - three times per week - and by further increments of 20 IU/kg if needed, three times per week, at monthly intervals.

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

2. Maintenance phase
To maintain a target Hb value of approximately 10-12 g/dl, the dosage is initially reduced to half of the previously administered amount. Subsequently, the dose is adjusted at intervals of two to four 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.

- Men: blood volume [ml] = 44 [ml/kg] x body weight [kg] + 1600 [ml] (body weight ≥ 45 kg)

The indication for Recormon treatment 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.



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.

Prevention of anemia of prematurity
For this indication, only solution for injection in pre-filled syringes may be used.

The solution is administered subcutaneously at a dose of 3 x 250 IU/kg b.w. per week. Recormon treatment should start as early as possible, preferably by day 3 of life. Premature infants who have received a transfusion before starting Recormon treatment are not likely to benefit as much as infants who have not had a transfusion. The treatment should last for 6 weeks.

2.2.1 Special Dosage Instructions

Children and adolescents:
Results of clinical studies in children and adolescents 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 (see section 2.5.4 Pediatric use).

Elderly:
No dedicated studies in elderly patients were performed. A large proportion of elderly patients were included in clinical trials with Recormon. A need for special dose adjustments in the elderly population was not identified.

2.3 Contraindications

Recormon is contraindicated in patients with:
- Hypersensitivity to the active substance or any of the excipients.
- Poorly controlled hypertension

In the indication "increasing the yield of autologous blood", Recormon 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

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 symptomatic anemia in cancer patients receiving chemotherapy:
The reconstituted solution is administered subcutaneously; 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).
Recormon treatment is indicated if the hemoglobin value is ≤ 11 g/dl (6.83 mmol/l). Hemoglobin levels should not exceed 13 g/dl (8.07 mmol/l) (see section 3.1.2 Clinical / Efficacy Studies).

If, after 4 weeks of therapy, the hemoglobin value has increased by at least 1 g/dl (0.62 mmol/l), the current dose should be continued. If the hemoglobin 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 hemoglobin 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 hemoglobin at that level. If required, further dose reduction may be instituted to ensure that hemoglobin level does not exceed 13 g/dl.

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

Treatment for increasing the amount of autologous blood:
The reconstituted 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.
2. The required amount of pre-donated blood is expressed in units whereby one unit in the nomogram is equivalent to 180 ml red cells.
3. 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]

thromboembolic disease.

Multidose/cartridges only:
The solvent contains benzyl alcohol as a preservative and must therefore not be used in infants or young children up to three years old.

2.4 Warnings and Precautions

2.4.1. General

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.

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.

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

Lack of effect: The most common reasons for incomplete response to ESAs are iron deficiency and chronic inflammation (e.g. due to uremia or advanced metastatic cancer). The following conditions may also compromise the effectiveness of ESAs therapy: chronic blood loss, bone marrow fibrosis, severe aluminium overload due to treatment of renal failure, folic acid or vitamin B_{12} deficiencies, and hemolysis. If all the conditions mentioned are excluded and the patient has a sudden drop of hemoglobin associated with reticulocytopenia and anti-erythropoietin antibodies, examination of the bone marrow for the diagnosis of Pure Red Cell Aplasia (PRCA) should be considered. If PRCA is diagnosed, therapy with epoetin beta must be discontinued and patients should not be switched to another ESA.

Pure red cell aplasia caused by neutralizing 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 2.6 Undesirable Effects).

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

A controlled clinical study in which epoetin beta was administered to patients with head and neck cancer, has shown a shorter locoregional progression free survival in patients receiving epoetin beta. Another clinical study in breast cancer designed to show a positive effect of epoetin beta on overall survival compared to untreated controls, showed no statistically significant effects in terms of overall survival or tumor progression. Furthermore, meta-analysis data from randomized, controlled clinical studies with epoetin beta in treatment of anemia in cancer patients (12 studies, 2301 patients; including the two studies mentioned above) did not show any statistically significant negative effects on survival or tumor progression (see section 3.1.2 Clinical / Efficacy Studies).

In *CKD patients and patients with cancer receiving chemotherapy* an increase in blood pressure (hypertensive episodes) or aggravation of existing hypertension, especially in cases of rapid Hb increase can occur. Increases in blood pressure can be treated with antihypertensive drugs. If blood pressure rises cannot be controlled by drug therapy, a transient interruption of Recormon therapy is recommended. Particularly at the beginning of therapy, regular monitoring of the blood pressure is

recommended, including between dialyses in patients with renal anemia. In patients with CKD, hypertensive crisis with encephalopathy-like symptoms may also occur in individual patients with otherwise normal or low blood pressure. This requires 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 aluminium overload due to treatment of renal failure may compromise the effectiveness of Recormon.

In *CKD* patients an increase in heparin dose during hemodialysis is frequently required during the course of therapy with Recormon as a result of the increased Hb. Occlusion of the dialysis system is possible if heparinization is not optimal. Early shunt revision and thrombosis prophylaxis by administration of acetylsalicylic acid, for example, should be considered in CKD patients at risk of shunt thrombosis.

In *CKD* 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.

In patients in an *autologous blood pre-donation program* 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.

For use of Recormon in an autologous pre-donation program, the official guidelines on principles of blood donation must be considered, in particular:
- only patients with a PCV ≥ 33 % (hemoglobin ≥ 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.

In patients treated for *anemia of prematurity*, there may be a slight rise in platelet counts, particularly up to day 12 - 14 of life, therefore platelets should be monitored regularly.

2.4.2 Drug Abuse and Dependence
Misuse by non-anemic persons may lead to an excessive increase in Hb. This may be associated with life-threatening complications of the cardiovascular system.

There are no reports on dependence when using epoetin beta.

2.4.3 Ability to Drive and Use Machines
No studies on the effects on the ability to drive and use machines have been performed. However, no effects are expected based on the mechanism of action and the known safety profile of Recormon.

2.4.4 Laboratory Tests
Platelet counts and hematocrit/hemoglobin levels should be monitored at regular intervals in all patients (see section 2.4.1 General, Warnings and Precautions).

2.5.7 Hepatic Impairment
No dedicated clinical trials were conducted in patients with hepatic impairment.

2.6 Undesirable Effects

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

Anemic patients due to chronic kidney disease
The most frequent adverse drug reactions (common 1-10%), in particular during the early treatment phase with Recormon are hypertensive events including hypertension, hypertensive crisis with or without encephalopathy-like symptoms (e.g. headaches and confused state, sensorimotor disorders - such as speech disturbance or impaired gait - up to tonoclonic seizures). These increases in blood pressure can occur in normotensive patients or can be an aggravation of existing hypertension (see section 2.4.1 General, Warnings and Precautions).

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 2.4.1 General-Warnings and Precautions). In most cases, a fall in serum ferritin values simultaneous with a rise in Hb is observed. In addition, transient increases in serum potassium and phosphate levels have been observed in isolated cases.

The incidences of adverse drug reactions in clinical trials are shown in the table below. The table shows the difference in frequencies of adverse events between patients receiving Recormon and control.

System Organ Class	Adverse Drug Reaction	Incidence
Vascular disorders	Hypertension	Common (>1%, <10%)
Vascular disorders	Hypertensive crisis	Uncommon (>0.1%, <1%)
Nervous system disorders	Headache	Common (>1%, <10%)
Blood and the lymphatic system disorders	Shunt thrombosis	Rare (>0.01%, <0.1%)
Blood and the lymphatic system disorders	Thrombocytosis	Very rare (<0.01%)

Cancer patients receiving chemotherapy with symptomatic anemia
Hypertensive events are common (1-10%) adverse drug reactions, in particular during the early phase of treatment.

In some patients, a fall in serum iron parameters is observed.

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 (both "common"); this is not associated with any increase in thromboembolic mortality compared with controls.

The incidences of adverse drug reactions in clinical trials are shown in the table below. The table shows the difference in frequencies of adverse events between patients receiving Recormon and control.

System Organ Class	Adverse Drug Reaction	Incidence

reported in patients receiving Recormon, though causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to interrupting Recormon administration until the level has been corrected.

2.4.5 Interactions with other Medicinal Products and other Forms of Interaction

No dedicated clinical interaction studies have been performed.

Clinical experience has not given evidence for potential interaction of Recormon with other medicinal products (for more information see also section 3.3. Preclinical Safety).

2.5 Use in Special Populations

2.5.1 Pregnancy

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development (see section 3.3 Preclinical Safety).

For epoetin beta, all safety information with regard to exposure to Recormon during pregnancies has 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/fetal development or postnatal development and treatment with Recormon. However in the absence of clinical study data, caution should be exercised when prescribing to pregnant women.

2.5.2 Labor and Delivery

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development (see section 3.3 Preclinical Safety).

For epoetin beta, all safety information with regard to exposure during labor and delivery has been gained from post marketing experience. No evidence of harmful effects with respect to labor and delivery have been observed. However in the absence of clinical study data, caution should be exercised when prescribing to pregnant women in labor.

2.5.3 Nursing Mothers

Only limited experience in human lactation has been gained. Endogeneous erythropoietin is excreted in breast milk and readily absorbed by the neonatal gastrointestinal tract. A decision on whether to continue or discontinue breast-feeding or to continue or discontinue therapy with epoetin beta should be made taking into account the benefit of breastfeeding to the child and the benefit of epoetin beta therapy to the woman.

2.5.4 Pediatric Use

Clinical registration trials have been performed in children and adolescents with anemia due to chronic kidney disease and in neonates for prevention of anemia due to prematurity.

In the indication anemia due to chronic kidney disease, Recormon should not be used in infants (i.e. below 2 years of age) (see sections 2.2.1 Special Dosage Instructions, 2.4.1 General, Warnings and Precautions).

In the indications anemia in cancer patients receiving chemotherapy and treatment for increasing the amount of autologous blood, Recormon is not indicated in the pediatric population.

2.5.5 Geriatric Use

See section 2.2.1 Special Dosage Instructions.

2.5.6 Renal Impairment

See section 2.2.1 Special Dosage Instructions.

Vascular disorders	Hypertension	Common (>1%, <10%)
Blood and the lymphatic system disorders	Thromboembolic event	Common (>1%, <10%)
Nervous system disorders	Headache	Common (>1%, <10%)

Patients in an autologous blood pre-donation program

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

A temporary iron deficiency may occur (see section 2.4.1 General, Warnings and Precautions).

The incidences of adverse drug reactions in clinical trials are shown in the table below. The table shows the difference in frequencies of adverse events between patients receiving Recormon and control.

System Organ Class	Adverse Drug Reaction	Incidence
Nervous system disorders	Headache	Common (>1%, <10%)

Premature infants

A fall in serum ferritin values is very common (>10%) (see section 2.4.1 General, Warnings and Precautions).

All indications

Rarely (≥1/10,000 to ≤1/1,000), skin reactions such as rash, pruritus, urticaria or injection site reactions may occur. In very rare cases (≤1/10,000) anaphylactoid reactions have been reported. However, in controlled clinical studies no increased incidence of hypersensitivity reactions was found.

In very rare cases (≤1/10,000), 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 or moderate in nature and subsided after a couple of hours or days.

2.6.1.1 Laboratory Abnormalities

See sections 2.4.1 General-Warnings and Precautions, 2.4.4 Laboratory Tests

2.6.2 Post Marketing

In isolated cases, neutralizing anti erythropoietin antibody-mediated pure red cell aplasia (PRCA) associated with Recormon therapy has been reported (see section 2.4 Warnings and Precautions).

With the exception of anti erythropoietin antibody-mediated pure red cell aplasia (PRCA), the safety information collected during post marketing experience reflects the expected adverse event profile in these populations and the ADR profile of epoetin beta (see sections 2.4.1 General, Warnings and Precautions, 2.5 Use in Special Populations, 2.6 Undesirable Effects).

2.6.2.1 Laboratory Abnormalities

Laboratory abnormalities reported during post marketing reflect the experience gained from clinical trials (see sections 2.4.1 General, Warnings and Precautions, 2.6.1 Clinical Trials).

2.7 Overdose

The therapeutic range of Recormon is wide and individual response to therapy must be considered when Recormon treatment is initiated. Overdose can result in manifestations of an exaggerated pharmacodynamic effect, e.g. excessive erythropoiesis which may be associated with life-threatening complications of the cardiovascular system. In case of excessive haemoglobin levels, Recormon should be temporarily withheld (see section 2.2 Dosage and Administration). If clinically indicated, phlebotomy may be performed.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

The biological efficacy of epoetin beta has been demonstrated after intravenous and subcutaneous administration in various animal models *in vivo* (normal and uremic rats, polycythemic 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 behavior or locomotor activity of mice and circulatory or respiratory function of dogs were observed.

3.1 Pharmacodynamic Properties

Epoetin beta is identical in its amino acid and carbohydrate composition to erythropoietin that has been isolated from the urine of anemic patients.

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

3.1.1 Mechanism of Action

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

3.1.2 Clinical / Efficacy Studies

This section describes recently completed randomized, controlled studies with epoetin beta in patients with renal anemia or cancer patients receiving chemotherapy/ radiotherapy.

Patients with anemia due to chronic kidney disease

An open randomized study using epoetin beta was conducted in 605 pre-dialysis patients (CREATE) with mild to moderate anemia (Hb level: 11-12.5 g/dl). The primary objective was to explore whether high Hb correction (13–15 g/dl) would reduce cardiovascular (CV) morbidity as compared with standard anemia treatment (target Hb 10.5–11.5 g/dl). There was no benefit observed with high Hb correction compared to standard anemia correction. On the contrary, there were fewer events observed in the standard treatment group (47 versus 58 events, HR 0.78, p=0.20). A difference in time to initiation of dialysis was observed favoring the standard anemia correction group (111 and 127 events, median time to dialysis 41 months and 36 months, log rank test p=0.034, respectively), although no difference in median creatinine clearance over time between the two study groups was observed. Quality of life (assessed by SF-36 Health Survey Questionnaire) was significantly improved (p=0.003) in the high target Hb group at 1 year.

In another open randomized study in 172 patients with early diabetic nephrology, (ACORD) the effect of high Hb correction (target Hb 13-15 g/dl) and standard Hb correction (target Hb 10.5-11.5 g/dl) on cardiac structure and function was investigated.

At the end of the study, there was no significant difference between the two groups with respect to the primary parameter, the baseline adjusted left ventricular mass index (p=0.88). There was no statistically significant difference between the treatment groups in change from baseline in calculated creatinine clearance, time to doubling of serum creatinine, or an analysis of rapid progressors. The General Health score of the quality of life assessment (using the SF-36 Health Survey Questionnaire) was significantly improved (p=0.04) in the high target Hb group.

3.2.2 Distribution

Pharmacokinetic investigations in healthy volunteers and uremic patients show that the distribution volume corresponds to one to two times the plasma volume.

3.2.3 Elimination

Pharmacokinetic investigations in healthy volunteers and uremic patients show that the half-life of intravenously administered epoetin beta is between 4 and 12 hours.

After subcutaneous administration of epoetin beta to uremic patients, the terminal half-life is higher than after intravenous administration, with an average of 13 - 28 hours.

3.2.4 Pharmacokinetics in Special Populations

No formal study of the effect of hepatic impairment on the pharmacokinetics of epoetin beta was conducted.

3.3 Preclinical Safety

3.3.1 Carcinogenicity

A carcinogenicity study with homologous erythropoietin in mice did not reveal any signs of proliferative or tumorigenic potential.

3.3.2 Other

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and toxicity of reproduction.

4. PHARMACEUTICAL PARTICULARS

4.1 Storage

Store in a refrigerator (2°C – 8°C).

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

Lyophilisate and solvent for solution for injection:

For the purpose of ambulatory use, the patient may remove the unreconstituted product from the refrigerator and store it at room temperature (not above 25°C) for one single period of up to 5 days.

Leaving the reconstituted solution outside the refrigerator should be limited to the time necessary for preparing the injections.

Chemical and physical in-use stability of the reconstituted solution has been demonstrated for one month at 2°C - 8°C. From a microbiological point of view, once opened, the reconstituted solution may be stored for maximum of one month at 2°C - 8°C. Other in-use storage times and conditions are the responsibility of the user.

Powder and solvent for solution for injection in cartridge:

For the purpose of ambulatory use, the patient may remove the cartridge not yet inserted into the Reco-Pen from the refrigerator and store it at room temperature (not above 25°C) for one single period of up to 5 days.

Chemical and physical in-use stability of the reconstituted solution has been demonstrated for one month at 2°C-8°C. From a microbiological point of view, once opened, the reconstituted solution may be stored for maximum of one month at 2°C-8°C. Other in-use storage times and conditions are the responsibility of the user.

After insertion into the Reco-Pen, the cooling chain may only be interrupted for administration of the product.

Solution for injection in pre-filled syringes:

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

Cancer patients with symptomatic anemia receiving chemotherapy

In a placebo-controlled study using epoetin beta in 351 patients with head and neck cancer (ENHANCE), study drug was administered to maintain the hemoglobin levels of 14 g/dl in women and 15 g/dl in men. Locoregional progression free survival was significantly shorter in patients receiving epoetin beta (HR=1.62, p=0.0008). The results and interpretation of this study were confounded by imbalances between the treatment groups, especially with regard to tumor localization, smoking status and the heterogeneity of the study population.

A controlled, open-label, randomized study using epoetin beta in 463 patients with metastatic breast cancer receiving chemotherapy (BRAVE), which was designed to show a significant improvement in survival, did not show any statistically significant difference between the control and epoetin beta arms with regards to overall survival (p=0.52) or time to tumor progression (p=0.45). A greater number of patients in the control arm (64/232; 27.6%) had transfusion and severe anemic events compared with the epoetin beta arm (40/231; 17.3%) (p=0.009), reflecting the efficacy of epoetin beta treatment with respect to preventing transfusions by effective increase in hemoglobin.

A higher percentage of epoetin beta patients experienced thromboembolic events (TEEs) during the study compared with the control arm (13% versus 6%) and a shorter time to TEE for the epoetin beta treatment arm compared with control (p=0.008) was seen. However, the percentage of patients that experienced a serious TEE (3% control versus 4% epoetin beta) or TEE leading to death (2% in each arm) was comparable.

A controlled, open label, randomized study using epoetin beta in 74 patients with cervical cancer receiving radiochemotherapy (MARCH) did not show a correlation between hemoglobin increase and the reduction in treatment failures (response to radiochemotherapy). Therefore, it was decided not to proceed this study to its second stage.

A meta-analysis including all controlled clinical studies in anemic cancer patients treated with epoetin beta was performed (12 studies with a total of 2301 patients). The results from this present meta-analysis confirm the known efficacy of epoetin beta with respect to increases in hemoglobin levels and a reduced risk of blood transfusion.

In the overall population including also patients with Hb initiation levels up to 13 g/dl, no statistically significant increase in risk of death in the epoetin beta group compared with the control group (HR: 1.13, 95% CI 0.87 to 1.46, p=0.34) was observed. In patients with baseline hemoglobin ≤ 11 g/dl, the HR for overall survival was 1.09 (95 % CI 0.80 to 1.47, p=0.58). For time to disease progression the HR was 0.85 (95% CI: 0.72 to 1.01, p=0.07). in the overall patient population. When the analysis was restricted to patients with baseline hemoglobin ≤ 11 g/dl the HR was 0.80 (95% CI 0.65 to 0.99, p=0.04).

This meta analysis also confirmed the increased rate of thromboembolic events (TEE) reported (see section 2.6.1 Clinical Trials-Undesirable Effects) with a TEE rate of 7% in the epoetin beta group compared with 4% in the control group.

3.2 Pharmacokinetic Properties

Pharmacokinetic investigations in healthy volunteers and uremic 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 uremic and normal rats.

3.2.1 Absorption

After subcutaneous administration of epoetin beta to uremic patients, the protracted absorption results in a serum concentration plateau, whereby the maximum concentration is reached after an average of 12 - 28 hours.

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

4,2 Special Instructions for Use, Handling and Disposal

Lyophilisate and solvent for solution for injection:

Incompatibilities

This medicinal product must not be diluted or mixed with other medicinal products except those mentioned below (content of accompanying solvent ampoule).

Instructions for use and handling and disposal

Recormon Multidose is supplied as a powder for solution for injection in vials. This is dissolved with the contents of the accompanying solvent ampoule by means of a reconstitution and withdrawal device according to the instructions given below. Only solutions which are clear or slightly opalescent, colorless and practically free of visible particles may be injected. Do not use glass materials for injection, use only plastic materials.

This is a multidose preparation from which different single doses can be withdrawn over a period of 1 month after dissolution. To avoid the risk of contamination of the contents always observe aseptic techniques (i.e. use disposable sterile syringes and needles to administer each dose) and strictly follow the handling instructions below. Before withdrawing each dose disinfect the rubber seal of the withdrawal device with alcohol to prevent contamination of the contents by repeated needle insertions.

Preparation of Recormon Multidose solution

1. Take the vial with the freeze-dried substance out of the package. Write the date of reconstitution and expiry on the label (expiry is 1 month after reconstitution).
2. Remove the plastic cap from the vial.
3. Disinfect the rubber seal with alcohol.
4. Take the reconstitution and withdrawal device (which allows sterile air exchange) out of the blister and remove the protective cover from the spike.
5. Attach the device to the vial until the snap lock clicks home
6. Put the green needle on the syringe contained in the package and remove the needle cover.
7. Hold the OPC (One-Point-Cut) ampoule with the blue point upwards. Shake or tap the ampoule to get any fluid in the stem into the body of the ampoule. Take hold of the stem and snap off away from you. Withdraw all the solvent into the syringe. Disinfect the rubber seal of the device with alcohol.
8. Penetrate the seal with the needle to a depth of about 1 cm and slowly inject the solvent into the vial. Then disconnect the syringe (with needle) from the device.
9. Swirl the vial gently until the powder has dissolved. Do not shake. Check that the solution is clear, colorless and practically free from particles. Put the protective cap on the top of the device.
10. Before and after reconstitution Recormon Multidose must be stored at +2° to +8°C (refrigerator).

Preparation of a single injection

1. Before withdrawing each dose disinfect the rubber seal of the device with alcohol.
2. Place a 26G needle onto an appropriate single-use syringe (max.1 ml).
3. Remove the needle cover and insert the needle through the rubber seal of the device. Withdraw Recormon solution into the syringe, expel air from the syringe into the vial and adjust the amount of Recormon solution in the syringe to the dose prescribed. Then disconnect the syringe (with needle) from the device.
4. Replace the needle by a new one (the new needle should have the size which you normally use for injections).
5. Remove the needle cover and carefully expel air from the needle by holding the syringe vertically and gently pressing the plunger upwards until a bead of liquid appears at the needle tip.

For subcutaneous injection, clean the skin at the site of injection using an alcohol wipe. Form a skin fold by pinching the skin between the thumb and the forefinger. Hold the syringe near to the needle and insert the needle into the skin with a quick, firm action. Inject Recormon solution. Withdraw the needle quickly and apply pressure over the injection site with a dry, sterile pad.

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

Lyophilisate and solvent for solution for injection in cartridge:

Incompatibilities
Recormon in cartridge should only be used with the Reco-Pen.
In the absence of compatibility studies, this medicinal product should not be mixed with other medicinal products.

Instructions for use and handling and disposal
This Recormon presentation is a two-chamber cartridge containing powder for solution for injection and preserved solution. The ready-to-use solution is prepared by inserting the cartridge into the Reco-Pen. Prior to this a needle should be attached to the Reco-Pen. Only solutions which are clear or slightly opalescent, colorless and practically free of visible particles may be injected.

Please observe the instructions for use which are delivered with the Reco-Pen.

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

Solution for injection in pre-filled syringes:

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

Instructions for use and handling and disposal

First wash your hands!
1. Remove one syringe from the pack and check that the solution is clear, colorless 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.

4.3 Packs

Pre-filled syringes:
Recormon 500 IU, 1000 IU, 2000 IU, 3000 IU, 4000 IU, 5000 IU, 6000 IU, 10,000 IU, 20,000 IU
Syringes with solution for injection 6

Recormon 30,000 IU
Syringes with solution for injection 1, 4

Recormon Multidose vials:
1 vial with powder for solution for injection and 1 ampoule with preserved solvent, 1 reconstitution and withdrawal device, 1 needle 21 G 2, 1 disposable syringe (10 ml or 5ml).

Recormon Cartridges for Reco-Pen:
1 or 3 two-chamber cartridges
Pen needles

Roche recommends the use of "Needles for Reco-Pen®" (equivalent to "PenFine Universal
Click ®" needles).

Medicine: keep out of reach of children

Current at October 2007

Pre-filled syringes and Multidose vials:
Made for F. Hoffmann-La Roche Ltd, Basel, Switzerland
by Roche Diagnostics GmbH, Mannheim, Germany

Cartridges:
Made for F. Hoffmann-La Roche Ltd, Basel, Switzerland
by Vetter Pharma-Fertigung GmbH & Co KG, Ravensburg, Germany