SUMMARY OF PRODUCT CHARACTERISTICS

Recormon® pre-filled syringes

Epoetin beta

Composition

Active ingredient: epoetin beta.
Excipients: urea, sodium chloride, polysorbate 20, sodium dihydrogen phosphate, sodium monohydrogen phosphate, calcium chloride, glycine, leucine, isoleucine, threonine, glutamic acid, and phenylalanine.
1 pre-filled syringe contains 500 IU, 1000 IU, 2000 IU, 3000 IU or 5000 IU epoetin beta in 0.3 ml water for injections as a solution for injection.
1 pre-filled syringe contains 10,000 IU or 20,000 IU epoetin beta in 0.6 ml water for injections as a solution for injection.

Solution for subcutaneous or intravenous injection.

Pharmacotherapeutic group

Epoetin beta (recombinant human erythropoietin) is a hormone which stimulates the production of red blood cells.

Indications

Recormon in pre-filled syringe is indicated for
- treatment of anemia associated with chronic renal failure (renal anemia) 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.
- prevention and treatment of anemia in adult patients with solid tumours and treated with platinum-based chemotherapy prone to induce anemia (cisplatin: 75 mg/m^2/cycle, carboplatin: 350 mg/m^2/cycle).
- increasing the yield of autologous blood from patients in a pre-donation programme.

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).

Dosage and administration

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

Treatment of anemic patients with chronic renal failure
The 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 arteriovenous fistula at the end of dialysis.
For non-hemodialysed patients, subcutaneous administration should always be preferred in order to avoid puncture of peripheral veins.
The aim of treatment is to increase the packed cell volume (PCV) to 30-35% whereby the weekly increase should be at least 0.5%. A value of 35% should not be exceeded. In the presence of high blood pressure or existing blood vessel diseases, the weekly increase in the PCV and the target PCV should be determined individually taking into account the clinical picture. In some patients the optimum PCV may be below 30%.

The following dosage schedule should be applied unless otherwise prescribed.
Treatment with Recormon is divided into two stages.

1. Correction phase

- 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 packed cell volume is not adequate (< 0.5% 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 if further increments are needed they should be 20 IU/kg, 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 packed cell volume of between 30 and 35%, 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).

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.

Prevention of anemia of prematurity

The solution is administered subcutaneously at a dose of 3 x 250 IU/kg b.w. per week. Treatment with Recormon should start as early as possible, preferably by day 3 of life. Premature infants who have already been transfused by the start of treatment with Recormon are not likely to benefit as much as untransfused infants. The treatment should last for 6 weeks.

Treatment of patients with solid tumours

The solution is administered subcutaneously whereby the weekly dose can be divided into 3 to 7 single doses.

Treatment with Recormon is indicated if the hemoglobin value is ≤ 13 g/dl (8.07 mmol/l) at the start of chemotherapy. The recommended initial dose is 450 IU/kg body weight per week. If, after 4 weeks, a patient does not show a satisfactory response in terms of hemoglobin values, then the dose should be doubled. The therapy should be continued for up to 3 weeks after the end of chemotherapy.
If hemoglobin falls by more than 1 g/dl (0.62 mmol/l) in the first cycle of chemotherapy despite concomitant therapy with Recormon, further therapy may not be effective.
An increase in hemoglobin by more than 2 g/dl (1.24 mmol/l) per month or beyond 14 g/dl (8.79 mmol/l) should be avoided. If hemoglobin increases by more than 2 g/dl/month, the Recormon dose should first be reduced by 50%. If values exceed 14 g/dl (8.79 mmol/l) therapy with Recormon should be interrupted until a value ≤ 12 g/dl (7.45 mmol/l) is achieved and then restarted with 50% of the previous weekly dose.

Treatment for increasing the amount of autologous blood
The solution is administered intravenously over approximately 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 predonated blood and the endogenous red cell reserve:

1. The required amount of predonated blood depends on the anticipated blood loss, use, if any, 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 predonated 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.

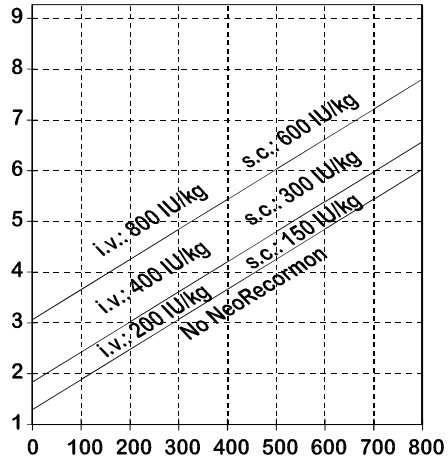
   Endogenous red cell reserve = blood volume [ml] x (PCV - 33) ÷ 100
   Women: blood volume [ml] = 41 [ml/kg] x body weight [kg] + 1200 [ml]

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 predonated blood and the endogenous red cell reserve according to the following graphs.

Female patients

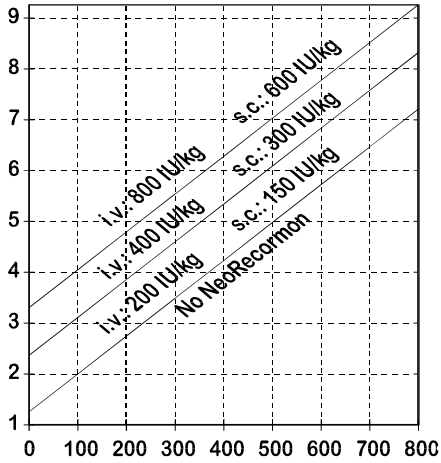
Required amount of predonated blood [units]



Endogenous red cell reserve [ml]

Male patients

Required amount of predonated blood [units]



Endogenous red cell reserve [ml]

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

Contraindications

Recormon must not be used in the presence of poorly controllable hypertension and known hypersensitivity to any of the constituents of the medication.
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 risk of deep venous thrombosis such as those with a history of venous thromboembolic disease.

Precautions

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

Animal experiments have yielded no indications of teratogenic effects of epoetin beta in dosing regimens that do not lead to an unphysiologically high PCV. No adequate experience in human pregnancy and lactation has been gained, but a potential risk appears to be minimal under therapeutic conditions.

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

Serum potassium levels should be monitored regularly during therapy with Recormon. Potassium elevation has been reported in a few uremic 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.

When using Recormon in the context of autologous blood donation, 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.

Special warnings

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

Undesirable effects

The following undesirable effects have been reported under therapy with Recormon. Please inform your physician or pharmacist about any other undesirable effects you experience in the course of Recormon treatment.

Cardiovascular system

Anemic patients with chronic renal failure: the most frequent adverse reaction during treatment with Recormon is an increase in blood pressure or aggravation of existing high blood pressure, especially if the PCV increases rapidly. These increases in blood pressure can be treated with drugs. If blood pressure rises cannot be controlled by drug therapy, a temporary interruption of Recormon therapy is recommended. Particularly at the beginning of therapy, regular monitoring of the blood pressure is recommended, including between dialyses. Hypertensive crisis with encephalopathy-like symptoms (e.g. headaches, confused state, disturbances of the senses and movement - such as speech disturbance or unsteady walking - up to convulsion [tonoclonic seizures]), 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.
Patients with solid tumours: occasionally, 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. Headache may also occur occasionally.

Blood

Anemic patients with chronic renal failure: 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. Development of thrombocytosis (too many platelets in the blood) is very rare. It is recommended that the platelet count is regularly monitored during the first 8 weeks of therapy.

An increase in heparin dose during hemodialysis 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.
Shunt thromboses (blockage of the shunt by blood clots) may occur, especially in patients who have a tendency to low blood pressure or whose arteriovenous fistulae exhibit complications (e.g. stenoses, aneurysms). Early shunt revision and measures to prevent blood clots by administration of acetylsalicylic acid, for example, are recommended in these patients.
In most cases, a fall in serum ferritin values simultaneously with a rise in packed cell volume is observed. Therefore, oral iron substitution of 200-300 mg Fe^{2+}/day is recommended in all patients with serum ferritin values below 100 µg/l or transferrin saturation below 20%. In addition, transient increases in serum potassium and phosphate levels have been observed in isolated cases. These parameters should be monitored regularly.

Premature infants: in most cases, a fall in serum ferritin values is observed. Therefore, oral iron treatment should begin as early as possible (by day 14 of life at the latest) with 2 mg Fe^{2+}/day. Iron dosing should be modified according to the serum ferritin level. If serum ferritin is below 100 µg/l or if there are other signs of iron deficiency, Fe^{2+} administration should be increased to 5-10 mg Fe^{2+} per day. Iron therapy should be continued until signs of iron deficiency disappear.
As there may be a slight rise in platelet counts, particularly up to day 12-14 of life, platelets should be monitored regularly.

Patients with solid tumours: in some patients, a fall in serum iron parameters is observed. Therefore, oral iron substitution of 200-300 mg Fe^{2+}/day is recommended in all patients with serum ferritin values below 100 µg/l or transferrin saturation below 20%.
Although no increase in the incidence of thromboembolic events has been observed in clinical trials, platelet counts should be monitored at regular intervals.

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 is determined at least once a week. 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.
Patients in an autologous blood donation 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.

As there are indications of a temporary iron deficiency, all patients should be treated orally with 300 mg Fe^{2+}/day from start of treatment with Recormon until ferritin values normalise. If, despite oral iron substitution, iron deficiency (ferritin below or equal to 20 µg/l or transferrin saturation below 20%) develops, the additional intravenous administration of iron should be considered.

Others

Rarely, skin reactions such as rash, pruritus, urticaria or injection site reactions may occur. In isolated cases, hypersensitivity reactions have been reported. However, in controlled clinical studies no increased incidence of hypersensitivity reactions was found.

Interactions

The clinical results obtained so far do not indicate any interaction of Recormon with other substances.

Animal experiments revealed that epoetin beta does not increase the myelotoxicity of cytostatic drugs like etoposide, cisplatin, cyclophosphamide, and fluorouracil.

Overdosage

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

Special remarks

Incompatibilities

To avoid incompatibility or loss of activity, do not mix with other drugs or infusion solutions.

Stability

Recormon in pre-filled syringe should not be used after the expiry date printed on the pack.

Recormon in pre-filled syringe must be stored continuously by the wholesaler/pharmacist in a refrigerator at a temperature of between 2°C and 8°C.

The patient must also store the product continuously in a refrigerator at a temperature of between 2°C and 8°C. For the purpose of ambulatory use the product may be removed from such storage for one single period of maximum 3 days at room temperature (up to 25°C).

Instructions for use

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.

Packs

Pre-filled syringes 500 IU	6
6 needles 30G1/2	
Pre-filled syringes 1000 IU, 2000 IU, 3000 IU, 5000 IU, 10,000, 20,000 IU	6
6 needles 27G1/2	

This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.

- Do not repeat the same prescription without consulting your doctor.

Medicine: keep out of the reach and sight of children

Council of Arab Health Ministers

Union of Arab Pharmacists

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