PFS-REC-2022 02-0

Recormon® pre-filled syringes

Epoetin beta

1. PHARMACEUTICAL FORM

Solution for injection (pre-filled syringes) (s.c. or i.v.).

Appearance: clear colourless to slightly opalescent solution.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: epoetin beta (synonyms: rhEPO, recombinant human erythropoietin).

Recormon 2000

1 pre-filled syringe contains 2000 international units (IU) (corresponding to 16.6 µg) epoetin beta in 0.3 ml water for injections.

Recormon 4000

1 pre-filled syringe contains 4000 international units (IU) (corresponding to 33.2 µg) epoetin beta in 0.3 ml water for injections.

Recormon 10 000

1 pre-filled syringe contains 10 000 international units (IU) (corresponding to 83 µg) epoetin beta in 0.6 ml water for injections.

Recormon 30 000

1 pre-filled syringe contains 30 000 international units (IU) (corresponding to 250 µg) epoetin beta in 0.6 ml water for injections.

List of excipients:

All presentations contain up to 0.3mg phenylalanine per pre-filled syringe (see section 2.4 Special Warnings and Precations for Use)

Clinical Particulars

2.1 Therapeutic Indications

Recormon 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.
- Treatment of symptomatic anemia in adult patients with non-myeloid malignancies receiving chemotherapy.
- Increasing the yield of autologous blood from patients in a predonation 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 to 13 g/dl [6.2 to 8.1 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; 5 or more units for males).

* Deficiency is defined as an inappropriately low serum erythropoietin level in relation to the degree of anemia.

2.2 Dosage 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.

Substitution by any other biological medicinal product requires the consent of the prescribing physician.

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 approximately 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 recommended hemoglobin target is 10 -12 g/dl. The target hemoglobin should be determined individually in the presence of hypertension or existing cardiovascular, cerebrovascular or peripheral vascular diseases. It is recommended that hemoglobin is monitored at regular intervals (e.g. every two to four weeks) until stabilised and periodically thereafter.

Treatment with Recormon is divided into two stages:

<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 body weight/week if the *Hb* increase is not adequate (*Hb < 1.5 g/L* 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.

<u>Maintenance phase</u>

To maintain hemoglobin between 10 – 12 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 pediatric clinical studies 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.

The dose for each patient should be adjusted so that the hemoglobin concentration does not exceed 12 g/dl. If the hemoglobin is increasing and approaching 12 g/dl, the dose should be reduced by approximately 25 -50%. If the hemoglobin continues to increase, the dose should be temporarily withheld until the hemoglobin begins to decrease, at which point therapy should be reinitiated at a dose approximately 25 - 50% below the previous dose. If the hemoglobin increases by more than 1 g/dl in any 2 week period, the dose should be decreased by approximately 25 - 50%.

Treatment of symptomatic anemia in cancer patients:

The solution is administered subcutaneously; the weekly dose can be given as one injection per week or in divided doses 3 to 7 doses times per week. The target hemoglobin concentration should be up to 12g/dl (7.45 mmol/l) and it should not be exceeded.

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

Recormon treatment is indicated if the hemoglobin value is ≤ 11 g/dl (6.83 mmol/l) at the start of chemotherapy. The recommended initial dose is 450 IU/kg body weight per week. 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 hemoglobin falls by more than 1 g/dl (0.62 mmol/l) in the first cycle of chemotherapy despite concomitant Recormon therapy, further therapy may not be effective.
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 for 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 12 g/dl.

If the rise in hemoglobin is greater than 2 g/dl (1.3mmol/l) in 4 weeks, the dose should be reduced by 25 to 50%.
It is recommended that hemoglobin is monitored at regular intervals (e.g. every two weeks) until stabilised and periodically thereafter.

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% or Hb 11g/dl, Recormon is administered at the end of blood donation.

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.

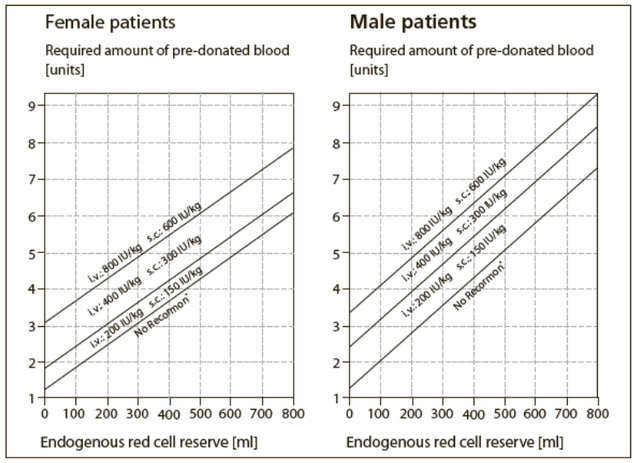
Endogenous red cell reserve = blood volume [ml] x (PCV - 33) ÷ 100

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 Recormon treatment 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.



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.

2.3 Contraindications

Recormon must not be used in the presence of poorly controllable hypertension and known hypersensitivity to the active substance or to any of the excipients.

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.

2.4 Special Warnings and Precautions for Use

In order to improve the traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

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.

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

The indication for Recormon treatment 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) 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. If anti-erythropoietin antibody-mediated PRCA develops whilst on Recormon, therapy with Recormon must be discontinued and patients should not be switched to another erythropoietin.

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 is regularly monitored during the first 8 weeks of therapy.

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.

Severe cutaneous adverse reactions (SCARs)
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 2.8). 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.

Effect on tumour growth

Epoetins are growth factors that primarily stimulate red blood cell production. Erythropoetin 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 any type of malignancy. Two controlled clinical studies in which epoetins were administered to patients with various cancers including head and neck cancer, and breast cancer, have shown an unexplained excess mortality.

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

ESAs, when administered to target hemoglobin of greater than 12 g/dl, shortened the time to tumour progression in patients with advanced head and neck cancer receiving radiation therapy. ESAs also shortened survival in patients with metastatic breast cancer receiving chemotherapy when administered to a target hemoglobin of greater than 12 g/dl.

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 could be determined at least once a week in these patients. If there is an increase in the 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 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.

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

For use of Recormon in an autologous blood predonation programme, 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 body 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 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.

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.

Laboratory tests

Platelet counts and haematocrit/haemoglobin levels should be monitored at regular intervals in all patients.

In patients with chronic kidney disease, serum potassium elevation has been 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.

2.5 Pregnancy and Lactation

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.

2.6 Effects on Ability to Drive and Use Machines

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

2.7 Undesirable Effects

Based on results from clinical trials including 1725 patients approximately 8% of patients treated with Recormon are expected to experience adverse reactions. Undesirable effects during treatment with Recormon are observed predominantly in patients with chronic renal failure or underlying malignancies and are most commonly an increase in blood pressure or aggravation of existing hypertension and headache.

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 2.4).

- **Cardiovascular system**

Anemic patients with chronic renal failure:

The most frequent undesirable effect during treatment with Recormon is an increase in blood pressure or aggravation of existing hypertension, especially in cases of rapid PCV increase. 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 the beginning of therapy, regular monitoring of blood pressure is recommended, including between dialyses.

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 occur, also 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 cancer:

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:

Shunt thromboses may occur, especially in patients who have a tendency to hypotension or whose arteriovenous fistulae exhibit complications (e.g. stenoses, aneurysms), see section 3.4 Special Warnings and Special Precautions. In most cases, a fall in serum ferritin values simultaneous with a rise in packed cell volume is observed.

Therefore, oral iron substitution of 200 to 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.

In very rare cases, neutralising anti-erythropoietin antibodies with or without pure red cell aplasia (PRCA) occurred during rHuEPO therapy. In case PRCA is diagnosed, therapy with erythropoietin must be discontinued and patients should not be switched to another erythropoietic substance.

Premature infants:

In most cases, a fall in serum ferritin values is observed.

Patients with cancer:

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 %. In patients with multiple myeloma, non-Hodgkin's lymphoma or chronic lymphocytic leukemia, with transferrin saturation below 25%, 100mg intravenous Fe^{3+} /week has also been used.

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 incidente is 5.9% compared to 4.2% in controls; this is not associated with any increase in thromboembolic mortality compared with controls.

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 Recormon treatment 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 Recormon treatment up to normalisation of ferritin values. 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, anaphylactoid reactions have been reported. However, in controlled clinical studies no increased incidence of hypersensitivity reactions was found.

In isolated cases, 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.

Tabulated summary of adverse drug reactions from clinical trials:

Adverse drug reactions from clinical trials (Table 1, Table 2 and Table 3) are listed by MedDRA system organ class. The corresponding frequency category for each adverse drug reaction is based on 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 <1/1000), very rare (<1/10,000).

Table 1: Adverse drug reactions occurring in anemic patients due to chronic kidney disease, treated with Recormon

System Organ Class	Frequency Category
Vascular Disorders	
Hypertension	Common
Hypertensive crisis	Uncommon
Nervous System Disorders	
Headache	Common
Blood and Lymphatic System Disorders	
Shunt thrombosis	Rare
Thrombocytosis	Very rare

Table 2: Summary of adverse drug reactions occurring in cancer patients receiving chemotherapy with symptomatic anaemia treated with Recormon

System Organ Class	Frequency Category
Vascular Disorders	
Hypertension	Common
Nervous System Disorders	
Headache	Common
Blood and Lymphatic System Disorders	
Thromboembolic event	Common

Table 3: Summary of adverse drug reactions occurring in patients in autologous blood predonation programme treated with Recormon

System Organ Class	Frequency
Nervous System Disorders	
Headache	Common

2.8 Postmarketing Experience

The following adverse drug reactions have been identified from postmarketing experience with Recormon (Table 4). Adverse drug reactions are listed according to system organ classes in MedDRA and the corresponding frequency category estimation for each adverse drug reaction is based on 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 <1/1000), very rare (<1/10,000), unknown (cannot be estimated from the available data).

Table 4: Adverse drug reactions from postmarketing experience

System Organ Class	Frequency
Blood and Lymphatic System Disorders	
Aplasia Pure Red Cell [1,2]	Unknown
Skin and Subcutaneous Tissue Disorders	
Stevens-Johnson syndrome/toxic epidermal necrolysis[2]	Unknown

[1] see section 2.4

[2] Incidence rate and frequency category cannot be estimated based on available data.

2.9 Overdose

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

2.10 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 3.3.5 Nonclinical Safety).

In animal experiments epoetin did not increase the myelotoxicity of cytostatic medicinal products like etoposide, cisplatin, cyclophosphamide, and fluorouracil.

3. PHARMACOLOGICAL PROPERTIES & EFFECTS

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.
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 behaviour or locomotor activity of mice and circulatory or respiratory function of dogs were observed.
Erythropoetin is a growth factor that primarily stimulates red cell production. Erythropoetin receptors may be expressed on the surface of a variety of tumour cells. There is insufficient information to establish whether the use of epoetin products have an adverse effect on time to tumour progression or progression free survival.

Two studies explored the effect of epoetins on survival and/or tumour progression with higher hemoglobin targets.

In a randomised placebo-controlled study using epoetin alfa in 939 metastatic breast cancer patients study drug was administered to attempt to maintain hemoglobin levels between 12 and 14 g/dl. At four months, death attributed to disease progression was higher (6% vs 3%) in women receiving epoetin alfa. The overall mortality was significantly higher in the epoetin alfa arm.

In another placebo-controlled study using epoetin beta in 351 patients with head and neck cancer, 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. The results of this study were confounded by imbalances between the treatment groups, especially with regard to tumour localization, smoking status and the heterogeneity of the study population.

In addition, several other studies have shown a tendency to improved survival suggesting that epoetin has no negative effect on tumour progression.

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

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.

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 to 28 hours. The terminal half-life is higher than after intravenous administration, with an average of 13 to 28 hours.

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

3.3 Nonclinical Safety Data

Acute toxicity

The single intravenous administration of 6000 IU/kg b.w epoetin beta in the dog and in doses of 3; 30; 300; 3000 or 30,000 IU/kg b.w. in the rat did not lead to any detectable toxic damage.

Chronic toxicity

Toxic signs were not observed in 3-month toxicity studies in rats with doses of up to 10,000 IU/kg b.w. or in dogs with doses of up to 3000 IU/kg b.w. administered daily either subcutaneously or intravenously, with the exception

of fibrotic changes of the bone marrow which occurred if PCV values exceed 80%. A further study in dogs revealed that the myelofibrosis does not occur if the packed cell volume is kept below 60%. The observation of myelofibrosis is therefore irrelevant to the clinical situation in man.

Carcinogenicity

A carcinogenicity study with homologous erythropoetin in mice did not reveal signs of proliferative or tumourigenic potential.

Genotoxicity

Epoetin beta did not reveal any genotoxic potential in the Ames test, in the micronucleus test, in the *in vitro* HGPRT test of in a chromosomal abberation test in cultured human lymphocytes.

Reproductive toxicology

Studies on rats and rabbits showed no relevant evidence of embryotoxic, fetotoxic or teratogenic properties. No alteration of fertility was detected. A peri-postnatal toxicity study revealed no adverse effects in pregnant/ lactating females and on the development of conceptus and offspring.

4. PHARMACEUTICAL PARTICULARS

4.1 List of Excipients

Urea, sodium chloride, polysorbate 20, sodium dihydrogen phosphate, sodium monohydrogen phosphate, calcium chloride, glycine, leucine, isoleucine, threonine, glutamic acid, phenylalanine and water for injections.

4.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

4.3 Stability

Store at 2-8°C (in a refrigerator).

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 product from the refrigerator and store it at room temperature (not above 25°C) for one single period of up to 3 days.

Recormon should not be used after the expiry date (EXP) shown on the pack.

4.4 Special Precautions for Use and 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 is in the syringe 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.

4.5 Instructions for Disposal

The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

- Needles and syringes should never be reused.
- Place all used needles and syringes into a sharps container (puncture-proof disposable container).
- Keep this container out of the reach of children.
- Placing used sharps containers in the household waste should be avoided.

Dispose of the full container according to local requirements or as instructed by your healthcare provider.
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater, and disposal through household waste should be avoided. Use established ‘collection systems' if available in your location.

5. PACKS

Recormon 2000 IU, 4000 IU, 10 000 IU	
Syringes with solution for injection	6
Recormon 30 000IU	
Syringes with solution for injection	1, 4

Medicine: keep out of reach of children

Current at Feb 2022

F. Hoffmann-La Roche Ltd, Basel, Switzerland