SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

Recormon® 30 000 IU/0,6 mℓ Injection

COMPOSITION

Each syringe contains 30 000 IU equivalent to 250 µg epoetin beta (recombinant human erythropoietin) as a solution for injection.

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

PHARMACOLOGICAL CLASSIFICATION

A 8.3 Erythropoietics

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Erythropoietin is a glycoprotein that stimulates, as a mitosis stimulating factor and differentiating hormone, the formation of erythrocytes from precursors of the stem cell compartment.

The rh-EPO obtained by gene technology is identical in its amino acid and carbohydrate composition to erythropoietin that has been isolated from the urine of anaemic patients.

The biological efficacy of rh-EPO has been demonstrated in various animal models *in vivo* (normal and uraemic rats, polycythaemic mice). After administration of rh-EPO, 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 rh-EPO.

Investigations in cell cultures of human bone marrow cells showed that rh-EPO stimulates erythropoiesis specifically and does not affect leucopoiesis. Cytotoxic actions of rh-EPO on bone marrow cells could not be detected.

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

Pharmacokinetic properties

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

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

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

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

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

INDICATIONS

Recormon is indicated for:

- The replacement of erythropoietin in transfusion dependent patients with renal anaemia, requiring regular haemodialysis.
- The treatment of symptomatic renal anaemia in non-dialysed patients with chronic renal failure.
- Prevention of anaemia of prematurity in infants with a birth weight of 750 to 1 500 g and a gestational age of less than 34 weeks.
- Treatment of symptomatic anaemia in adult patients with non-myeloid malignancies receiving chemotherapy.
- Increasing the yield of autologous blood donated by patients scheduled for elective surgery. Its use in this indication must be balanced against the reported increased risk of thromboembolic events. Treatment should only be given to patients with moderate anaemia (Hb 10 - 12 g/dℓ) [6,21 - 7,44 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 and 5 or more units for males).

CONTRAINDICATIONS

Known hypersensitivity to epoetin beta or to any of the excipients in Recormon.

Recormon is contraindicated in the presence of poorly controlled hypertension.

The indication "increasing the yield in 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.

WARNINGS AND SPECIAL PRECAUTIONS

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

Clinical trials in anaemic patients with various cancers, including breast, head and neck cancer, have shown an unexplained increased mortality in patients who have received epoetins such as Recormon to increase haemoglobin concentrations beyond the level necessary to control symptomatic anaemia and to avoid blood transfusion. Evidence as to whether epoetins have a negative effect on time to tumour progression or progression-free survival is inconclusive.

- Recormon should be used with caution in the presence of refractory anaemia with excess blasts in transformation, epilepsy, thrombocytosis, chronic liver failure and known or suspected hypersensitivity to Recormon (see CONTRAINDICATIONS).
- Folic acid and vitamin B_{12} deficiencies should be ruled out, as they reduce the effectiveness of Recormon.

- Misuse by healthy persons (e.g. for doping) may lead to an excessive increase in packed cell volume. This may be associated with life-threatening complications of the cardiovascular system.
- 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.
- *Lack of effect:* The most common reasons for incomplete response to erythropoietin stimulating agents (ESAs) such as Recormon are iron deficiency and chronic inflammation (e.g. due to uraemia 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 haemolysis. If all the conditions mentioned are excluded and the patient has a sudden drop of haemoglobin associated with reticulocytopenia and anti-erythropoietin antibodies, examination of the bone marrow for the diagnosis of Pure Red Cell Aplasia (PRCA) should be considered. If PRCA is diagnosed, therapy with Recormon must be discontinued and patients should not be switched to another ESA.
- Pure red cell aplasia 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.
- *Effect on tumour growth:* Epoetins such as Recormon are growth factors that primarily stimulate red blood cell production. Erythropoietin receptors may be expressed on the surface of a variety of tumour cells. There is a concern that epoetins such as Recormon could stimulate the growth of any type of malignancy. Two controlled clinical studies in which epoetins such as Recormon

were administered to patients with various cancers including head and neck cancer, and breast cancer, have shown an unexplained excess mortality.

- In *chronic renal failure patients and patients with cancer receiving chemotherapy* an increase in blood pressure or aggravation of existing hypertension, especially in cases of rapid Hb increase can occur. These increases in blood pressure can be treated with medicines. If blood pressure rises cannot be controlled by drug therapy, a transient interruption of Recormon therapy is recommended. Particularly at beginning of therapy, regular monitoring of the blood pressure is recommended, including between dialyses. In chronic kidney disease patients hypertensive crisis with encephalopathy-like symptoms may also occur in patients with otherwise normal or low blood pressure. This requires the immediate attention of a medical practitioner and intensive medical care. Particular attention should be paid to sudden stabbing migraine like headaches as a possible warning sign.
- Severe aluminium overload, as a result of treatment of renal failure, may compromise the effectiveness of Recormon.
- In chronic renal failure patients an increase in heparin dose during haemodialysis is frequently required during the course of therapy with Recormon as a result of the increased Hb.
- Occlusion of the dialysis system is possible if heparinisation is not optimum. Early shunt revision and thrombosis prophylaxis by administration of acetylsalicylic acid (aspirin), for example, should be considered in chronic renal failure patients at risk of a shunt thrombosis.
- In chronic renal failure patients, there may be a moderate dose-dependent rise in platelet count within the normal range during treatment with Recormon, especially after intravenous administration. This reverts during the course of continued therapy. Development of thrombocytosis may occur. It is recommended that the platelet count be regularly monitored during the first eight 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. It is recommended that the platelet count be determined at least once a week. If there is an increase in platelets of more than 150 x 10^9/ℓ, or if the platelets rise above the normal range, treatment with Recormon should be discontinued.
- For use of Recormon in the course of autologous blood donation, the official guidelines on principles of blood donation must be considered, in particular:

  - only patients with a packed cell volume (PCV) ≥ 33 % (haemoglobin ≥ 11 g/dℓ) should donate;

  - special care should be taken with patients below 50 kg weight;

  - the single volume withdrawn should not exceed approximately 12 % of the patient's established 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 *anaemia 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.

  Laboratory tests
- Platelet counts and haematocrit/haemoglobin levels should also be monitored at regular intervals in all patients.
- In patients with chronic kidney disease, serum potassium levels should be monitored regularly during Recormon therapy. Potassium elevation has been reported in uraemic patients receiving Recormon, though causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to ceasing Recormon administration until the level has been corrected.

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

In the indication anaemia due to chronic kidney disease, Recormon should not be used in infants (i.e. below 2 years of age).

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

Effects on the 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.

Recormon contains up to 0,3 mg phenylalanine as an excipient. Therefore this should be taken into consideration in patients affected with severe forms of phenylketonuria.

INTERACTIONS

None known.

PREGNANCY AND LACTATION

Recormon must not be used during pregnancy and lactation.

DOSAGE AND DIRECTIONS FOR USE

Recormon prefilled syringe is supplied as a solution for injection ready for use. Only solutions which are clear or slightly opalescent, colourless and practically free of visible particles may be injected. Recormon prefilled syringe is a sterile but unpreserved product. Under no circumstances should more than one dose be administered per syringe; discard any unused portion.

The response to treatment with Recormon cannot be predicted. Monitoring of haemoglobin and platelets is thus imperative.

- ***Treatment of anaemic patients with chronic renal failure***

The reconstituted solution can be administered subcutaneously or intravenously. In case of intravenous administration, the solution should be injected over approximately 2 minutes, e.g. in haemodialysis patients via the arterio-venous fistula, at the end of dialysis.

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

In chronic kidney disease patients, the aim of treatment is to reach a target Hb level of 10 - 12 g/dℓ. In the presence of hypertension or existing cardiovascular, cerebrovascular or peripheral vascular diseases, the weekly increase in the 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 anaemia.

Treatment with Recormon is divided into two phases:

- 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 body weight, per week, if the increase of packed cell volume is not adequate (< 0,25 g/dℓ per week).

The weekly dose can also be divided into daily doses.

Intravenous administration:

The initial dose is 3 x 40 IU/kg body weight per week. To achieve a packed cell volume of between 30 and 35 %, the dosage may be raised, after one month, to 80 IU/kg body weight – three times per week – and by further increments of 20 IU/kg if needed, three times per week, at monthly intervals.

For both routes the maximum dosage should not exceed 720 IU/kg body weight per week.

- 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 in the correction phase. A haematocrit level of 35 % should not be exceeded. Subsequently, the dose is adjusted at intervals of 2 - 4 weeks individually for the patient (maintenance dose).

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

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.

- ***Prevention of anaemia of prematurity***

The solution is administered subcutaneously at a dose of 3 x 250 IU/kg body weight per week. Recormon treatment should start as early as possible, preferably at day 3 of life. Premature infants

who have already been transfused by the start of Recormon treatment are not likely to benefit as much as untransfused infants. The treatment should last for 6 weeks.

- ***Treatment of symptomatic anaemia 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 single 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 is indicated if the haemoglobin is < 11 g/dℓ (6,83 mmol/ℓ). Haemoglobin levels should not exceed 12 g/dℓ (7,44 mmol/ℓ).

If after 4 weeks of therapy, the haemoglobin value has increased by at least 1 g/ dℓ (0,62 mmol/ℓ), the current dose should be continued. If the haemoglobin value has not increased by at least 1 g/ dℓ (0,62 mmol/ℓ), a doubling of the weekly dose should be considered. If after 8 weeks of therapy, the haemoglobin value has not increased by at least 1,0 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 - 50 % in order to maintain haemoglobin at that level. If required further dose reduction may be instituted to ensure that the haemoglobin level does not exceed 12 g/dℓ (7,44 mmol/ℓ).

If the rise in haemoglobin is greater than 2 g/dℓ (1,3 mmol/ℓ) in 4 weeks, the dose should be reduced by 25 - 50 %.

- ***Treatment for increasing the yield of donated autologous blood***

The solution is administered intravenously over approximately 2 minutes, or subcutaneously.

Recormon is administered twice weekly over four 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. Assuming a PCV of 40 %, 200 mℓ red blood cell volume is equivalent to 500 mℓ whole blood or 300 mℓ erythrocyte concentrate.

   The required amount of pre-donated blood is expressed in units whereby one unit in the nomogram is equivalent to 180 mℓ red cells.

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

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

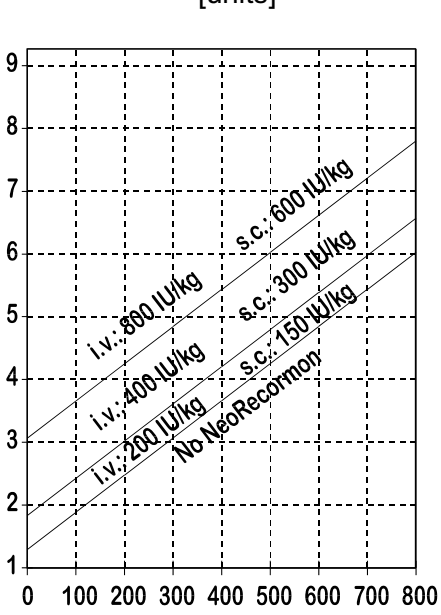
Men: blood volume [mℓ] = 44 [mℓ/kg] x body weight [kg] + 1 600 [mℓ]

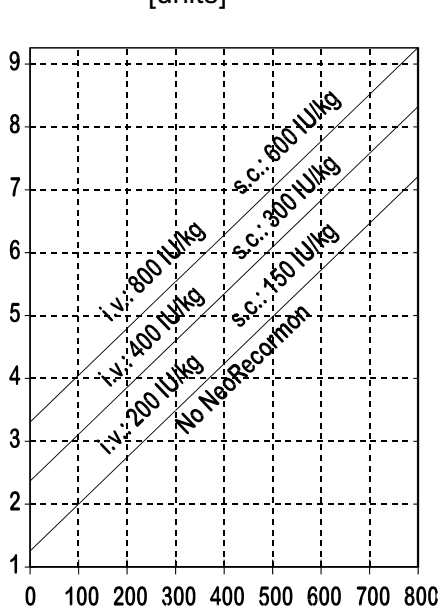
Women: blood volume [mℓ] = 41 [mℓ/kg] x body weight [kg] + 1 200 [mℓ]

(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:

Female patients	Male patients
Required amount of pre-donated blood	Required amount of pre-donated blood





The single dose thus determined is to be administered twice weekly, over 4 weeks. The maximum dose should not exceed 1 600 IU/kg body weight per week for intravenous use or 1 200 IU/kg per week for subcutaneous administration.

Special Dosage Instructions

Results of clinical studies in children have shown that children need significantly higher dosages than adults and that, on average, the younger the patients, the higher the epoetin beta doses required. Nevertheless, the recommended dosing schedule should be followed as the individual response cannot be predicted.

Instructions for use/handling

The following instructions for use should be read before using Recormon pre-filled syringe.

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 same compartment of 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 solution 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 the 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.

SIDE EFFECTS

Based on results from clinical trials including 1 725 patients approximately 8 % of patients treated with Recormon are expected to experience adverse reactions.

- *Anaemic patients with chronic renal failure*

The most frequent (common 1 - 10 %) adverse reaction during treatment with Recormon is an increase in blood pressure or aggravation of existing hypertension, especially in cases of rapid PCV increase. Hypertensive crisis with encephalopathy-like symptoms (e.g. headaches and confused state, sensorimotor disorders - such as speech disturbance or impaired gait - up to tonoclonic seizures) may also occur in individual patients with otherwise normal or low blood pressure.

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

The incidences of undesirable effects in clinical trials, considered related to treatment with Recormon are shown in the table below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	**Adverse Drug Reaction**	**Incidence**
Vascular disorders	Hypertensive crisis Hypertension	Uncommon (> 0,1 %, < 1 %) Common (> 1 %, < 10 %)
Nervous system disorders	Headache	Common (> 1 %, < 10 %)
Blood and the lymphatic system disorders	Shunt thrombosis Thrombocytosis	Rare (> 0,01 %, < 0,1 %) Very rare (< 0,01 %)

- *Patients with cancer*

Recormon treatment-related headache and hypertension which can be treated with medicines are common (> 1 %, < 10 %).

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 5,9 % compared to 4,2 % in controls; this is not associated with any increase in thromboembolic mortality compared with controls.

The incidences of undesirable effects in clinical trials, considered related to treatment with Recormon are shown in the table below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Adverse Drug Reaction	Incidence
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.

In placebo-controlled trials temporary iron deficiency was more pronounced in patients treated with Recormon than in controls.

The incidences of undesirable effects in clinical trials, considered related to treatment with Recormon are shown in the table below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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 %).

- *All indications*

Rarely (≥ 1/10 000 to ≤ 1/1 000), Recormon treatment-related skin reactions such as rash, pruritus, urticaria or injection site reactions may occur. In very rare cases (≤ 1/10 000), Recormon treatment-related 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, Recormon treatment-related flu-like symptoms such as fever, chills, headaches, pain in the limbs, malaise and/or bone pain have been reported. These reactions were mild or moderate in nature and subsided after a couple of hours or days.

Post Marketing Experience

Neutralising anti-erythropoietin antibody-mediated pure red cell aplasia (PRCA) associated with Recormon therapy has been reported.

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 adverse drug reaction profile of Recormon.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

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. Treatment is symptomatic and supportive. If clinically indicated, phlebotomy may be performed.

IDENTIFICATION

Colourless, glass syringe containing a colourless, clear to slightly opalescent solution.

PRESENTATION

Recormon 30 000 IU/0,6 mℓ: Packs containing 1 or 4 pre-filled syringes in an outer collapsible carton.

Not all pack sizes may be marketed.

STORAGE INSTRUCTIONS

Recormon pre-filled syringes must be stored in a refrigerator at a temperature of 2 °C to 8 °C. Do not freeze.

The cooling chain may only be interrupted for one single period to a maximum of 3 days at room temperature (25 °C).

KEEP OUT OF REACH OF CHILDREN.

Keep the syringe in the outer container to protect from light.

Do not use this product after the expiry date shown on the pack.

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 minimised. 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.

REGISTRATION NUMBER

Recormon 30 000 IU/0,6 mℓ: 39/8.3/0105

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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DATE OF PUBLICATION OF THE PACKAGE INSERT

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