

WARNING: To be supplied against the demand from Hospitals/Institutions for their use and against the prescription of a Specialist only

Epoetin beta Injection I.P.

NeoRecormon®

निंओरीकॉर्मन®

1. DESCRIPTION

1.1 Therapeutic / Pharmacologic Class of Drug

Antianemic agent

ATC code: B03XA

1.2 Type of Dosage Form and Strength

Type of dosage form:- Solution for injection (pre-filled syringes).

Strength:-

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

10,000 IU = 83 micrograms epoetin beta with 0.6 ml solution for injection

30,000 IU = 250 micrograms epoetin beta with 0.6 ml solution for injection

1.3 Route of Administration

Subcutaneous (s.c.) injection.

1.4 Sterile / Radioactive Statement

Sterile product.

1.5 Qualitative and Quantitative Composition

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

NeoRecormon is provided as solution for injection in pre-filled syringes.

2000 IU = 16.6 micrograms epoetin beta with 0.3 ml solution for injection

5000 IU = 41.5 micrograms epoetin beta with 0.3 ml solution for injection

List of excipients:

All presentations contain Urea, Sodium Chloride, Polysorbate 20, Sodium Dihydrogen Phosphate, Disodium Hydrogen Phosphate, Calcium Chloride, Glycine, L-Leucine, L-Isoleucine, L-Threonine, L-Glutamic acid, L-Phenylalanine (up to 0.3 mg per pre-filled syringe) and Water for injection. (see section 2.4.1 General, Warnings and Precautions).

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

Treatment of anemia due to chronic renal failure, and end stage renal diseases.

Treatment of symptomatic anemia in adult patients, with non-myeloid malignancies receiving chemotherapy.

Prevention of anemia of prematurity in infants with a birth weight of 750g to 1500g and a gestational age of less than 34 weeks.

Increasing the yield of autologous blood from patient in a pre-donation program.

2.2 Dosage and Administration

Therapy with NeoRecormon 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 NeoRecormon 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 (see section 4.2, Special Instructions for Use, Handling and Disposal).

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 NeoRecormon is used to provide adequate control of the symptoms of anemia.

Treatment with NeoRecormon 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*

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.

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.

Treatment with NeoRecormon 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).

NeoRecormon 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.

NeoRecormon is administered twice weekly over 4 weeks. On those occasions where the patient's PCV allows blood donation, i.e. PCV \geq 33 %, NeoRecormon 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:

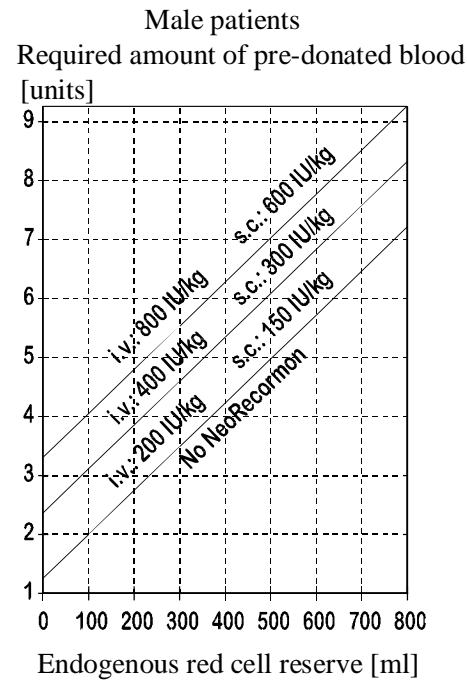
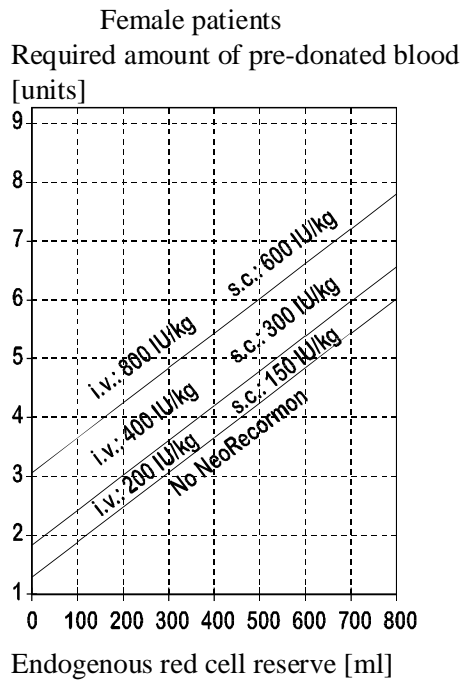
1. The required amount of pre-donated blood depends on the anticipated blood loss, use of blood conserving procedures and the physical condition of the patient.
This amount should be that quantity which is expected to be sufficient to avoid homologous blood transfusions.
2. The required amount of pre-donated 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) \div 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 \geq 45 kg)

The indication for NeoRecormon 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. NeoRecormon treatment should start as early as possible, preferably by day 3 of life. Premature infants who have received a transfusion before starting NeoRecormon 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

Pediatric use:

Results of pediatric clinical studies have shown that, on average, the younger the patients, the higher the NeoRecormon doses required. Nevertheless, the recommended dosing schedule should be followed as the individual response cannot be predicted (see section 2.5.4 Pediatric use).

Geriatric use:

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

Hepatic Impairment:

No dedicated clinical trials were conducted in patients with hepatic impairment. No special Dosage Instructions are available.

2.3 Contraindications

NeoRecormon is contraindicated in patients with:

- Known hypersensitivity to the active substance or any of the excipients.
- Poorly controlled hypertension

In the indication "increasing the yield of autologous blood", NeoRecormon 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 increased risk of deep venous thrombosis such as those with a history of venous thromboembolic disease.

2.4 Warnings and Precautions

2.4.1 General

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.

NeoRecormon 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 B₁₂ deficiencies should be ruled out as they reduce the effectiveness of NeoRecormon.

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.

NeoRecormon 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 B₁₂ 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 NeoRecormon. 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 NeoRecormon (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 NeoRecormon 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 NeoRecormon.

In *CKD patients* an increase in heparin dose during hemodialysis is frequently required during the course of therapy with NeoRecormon 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 NeoRecormon, 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 $150 \times 10^9/l$ or if platelets rise above the normal range, treatment with NeoRecormon should be discontinued.

For use of NeoRecormon in an autologous pre-donation program, the official guidelines on principles of blood donation must be considered, in particular:

- only patients with a PCV $\geq 33\%$ (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.

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

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

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

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 Nonclinical Safety).

For epoetin beta, all safety information with regard to exposure to NeoRecormon 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 NeoRecormon. 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 Nonclinical 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 Lactation

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, NeoRecormon 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, NeoRecormon 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 2.4.1 General - Warning and Precautions

2.5.7 Hepatic Impairment

(see section 2.2.1 Special Dosage Instructions).

2.6 Undesirable Effects

2.6.1 Clinical Trials

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

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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1000$), very rare ($< 1/10,000$).

Anemic patients due to chronic kidney disease

The most frequent adverse drug reactions (common 1-10%), in particular during the early treatment phase with NeoRecormon 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 tonic-clonic 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 NeoRecormon and control.

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

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

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 NeoRecormon compared to untreated controls or placebo. In patients treated with NeoRecormon, 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 NeoRecormon and control.

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

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

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 NeoRecormon 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 NeoRecormon and control.

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

System Organ Class	Frequency Category
Nervous System Disorders	
Headache	Common

Premature infants

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

All indications

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

In very rare cases ($\leq 1/10,000$), 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.

Laboratory Abnormalities

See section 2.4.1 General-Warnings and Precautions.

2.6.2 Postmarketing Experience

The following adverse drug reactions have been identified from postmarketing experience with NeoRecormon (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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ 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 Category	CDS reference
Blood and Lymphatic System Disorders		
Aplasia Pure Red Cell ^{1,2}	Unknown	3
Skin and Subcutaneous Tissue Disorders		
Stevens-Johnson syndrome / toxic epidermal necrolysis ²	Unknown	32

¹ see section 2.4

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

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 NeoRecormon is wide and individual response to therapy must be considered when NeoRecormon 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, NeoRecormon should be temporarily withheld (see section 2.2 Dosage and Administration). If clinically indicated, phlebotomy may be performed.

2.8 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 NeoRecormon 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 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 ⁵⁹Fe-incorporation rate.

An increased ³H-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.

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 \leq 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 \leq 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.

3.1.3 Immunogenicity

(see section 2.4.1 Warnings and Precautions, General).

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.

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 Metabolism

Not applicable.

3.2.4 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.

3.2.5 Pharmacokinetics in Special Populations

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

3.3 Nonclinical 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 Genotoxicity

Not applicable.

3.3.3 Impairment of Fertility

Not applicable.

3.3.4 Reproductive toxicity

Not applicable.

3.3.5 Other

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

4. DESCRIPTION

Epoetin Beta (EPO) is a glycoprotein that consists of 165 amino acids resulting in a molecular mass of 18 kDa of the protein part. The polypeptide chain is linked through two disulfide bridges, one between cysteins at position 7 and 161 and one between cysteins at position 29 and 33 in the amino acid sequence. Carbohydrates are attached to three asparagines at position 24, 38 and 83 and one serine at position 126. The molecular mass of the fully glycosylated EPO amounts to approximately 30 kDa.

NeoRecormon is a clear, colourless “ready-to-use” solution in a colourless glass syringe (type I) with a plunger stopper and a tip-cap.

All presentations contain Epoetin Beta, Urea, Sodium Chloride, Polysorbate 20, Sodium Dihydrogen Phosphate, Disodium Hydrogen Phosphate, Calcium Chloride, Glycine, L-Leucine, L-Isoleucine, L-Threonine, L-Glutamic acid, L-Phenylalanine (up to 0.3 mg per pre-filled syringe) and Water for injection.

5. PHARMACEUTICAL PARTICULARS

5.1 Storage

Store in a refrigerator (2°C – 8°C).

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

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

5.2 Special Instructions for Use, Handling and Disposal

Incompatibilities

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

Instructions for use and handling

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 NeoRecormon 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 NeoRecormon 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.

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.

5.3 Packs

The pack size for marketed strengths of NeoRecormon pre-filled syringe along with needle in India are:

2000 IU Prefilled Syringe:

One pack contains: 1 pre-filled syringe and 1 needle 27G1/2. The syringes are made of glass type I and the tip cap and plunger stopper of rubber material.

5000 IU Prefilled Syringe:

One pack contains: 1 pre-filled syringe and 1 needle 27G1/2. The syringes are made of glass type I and the tip cap and plunger stopper of rubber material.

5.4 Shelf Life

24 months when stored under recommended storage conditions.

Keep out of reach of children.

6. PATIENT COUNSELLING INFORMATION

Inform patients:

- Of the need to have regular laboratory tests for hemoglobin.
- Of the potential risk of tumor progression [*see section 2.4 Warnings and Precautions*]
- To undergo regular blood pressure monitoring, adhere to prescribed anti-hypertensive regimen and follow recommended dietary restrictions.
- To seek medical care immediately if they experience any symptoms of an allergic reaction with use of NeoRecormon
- To contact their healthcare provider for new-onset neurologic symptoms or change in seizure frequency.

Administer NeoRecormon under the direct supervision of a healthcare provider or, in situations where a patient has been trained to administer NeoRecormon at home, provide instruction on the proper use of NeoRecormon, including instructions to:

- Carefully review the Special Instructions for Use, Handling and Disposal.
 - Avoid the reuse of needles, syringes, or unused portions of the NeoRecormon single-dose prefilled syringes and properly dispose of these items.

Always keep a puncture-proof disposal container available for the disposal of used syringes and needles.

7. DETAILS OF MANUFACTURER

Manufactured by F. Hoffmann-La Roche Ltd, Grenzacherstrasse 124, CH-4070, Basel, Switzerland at

- 1) Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305, Mannheim, Germany.
OR

- 2) Vetter Pharma-Fertigung GmbH & Co. KG, Schützenstrasse 87 and 99-101, 88212 Ravensburg, Germany

[NOTE: Please refer outer carton and vial label for “manufactured by” details]

Imported and Marketed by:

Roche Products (India) Pvt. Ltd. C/O. Parekh Integrated Services Pvt Ltd, Gala No. A1, First Floor, Warehouse no. 6, BGR Logistics Park, NH-3, Zone 5, Bhiwandi, Maharashtra (India) – 421302

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8. DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE

Permission No.: 12-67/88-DC dated 19 September 1997

9. DATE OF REVISION

Current at January 2021; Version 5.0