THE EU RISK MANAGEMENT PLAN FOR NEORECORMON® / EPOETIN BETA

RMP version to be assessed as part of this application:

RMP Version number: 4.0

Data lock point for this RMP: 6 December 2023

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Date and Time (UTC)	Reason for Signing	Name
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Rationale for submitting an updated RMP:

This RMP is being updated in line with GVP Module V (Rev. 2) to fulfill the PRAC request from 2023 PBRER (1120020). Only risks that are likely to have an impact on the risk-benefit balance or, when further characterized and if confirmed, would have an impact on the risk-benefit balance should be maintained in the RMP as addressed in the current RMP update.

Summary of significant changes in this RMP:

- Table 1 within Part I (Product Overview) has been updated with respect to an update to indications in EEA along with medicinal products to which this RMP refers to, from ten to nine.
- Part II Module SI (Epidemiology of the Indications and target Populations) has been updated.
- PART II: Module SIV – (Populations not Studied in Clinical Trials): Rationale for the important exclusion criteria in pivotal studies in development program is updated in line with wording from core RMP v2.0.
- Part II Module SV. 1.2 (Exposure) has been updated with the cumulative post-marketing exposure until 31 January 2023 from PBRER 1120020.
- PART II: Module SVII (New Safety Concerns and re-classification with a Submission of an Updated RMP) and PART II: Module SVIII (Table 14-Summary of Safety Concerns) have been updated to reflect the updated risks.
- Part VII.3 (Details of Important Identified Risks, Important Potential Risks, and Missing Information) has been updated in line with the Summary of Safety concerns.
- Part III.2 Additional Pharmacovigilance has been updated with respect to milestones for Monitoring program for Anti-Erythropoietin Antibody mediated (AEAB-mediated) Pure Red Cell Aplasia (PRCA).
- Part V (Risk Minimization Measures (including Evaluation of the Effectiveness of Risk Minimization Activities) has been updated with removal of all safety concerns and their routine risk minimization activities except for AEAB-mediated PRCA (Renal Anemia).
- Annex 4 has been updated to include the specific adverse reaction follow-up for AEAB-mediated PRCA (Renal Anemia) via post-marketing active surveillance by a Guided Questionnaire.
- Annex 6 has been updated with the details of proposed additional risk minimization activities for antibody-mediated PRCA.
- Annex 7 has been updated to include the most recent data on pregnancy and lactation and post marketing exposure in line PBRER 1120020; data lock point of 13 February 2023.
- Annex 8 has been updated to reflect all changes made to the RMP.

Other RMP versions under evaluation:

Not applicable.

Details of Currently Approved RMP:

RMP Version number: 3.2

Approved with procedure: EMEA/H/C/000116/II/0083

Date of approval (opinion date): 23 July 2015

See page 1 for signature and date

PPD	Date

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PPD	Date

PART I: PRODUCT OVERVIEW

Table 1 Product Overview

Active Substance(s) (INN or common name)	Epoetin beta
Pharmacotherapeutic group(s) (ATC Code)	B03XA
Marketing Authorization Holder (or Applicant)	Roche Registration GmbH
Medicinal products to which this RMP refers	Nine
Invented name(s) in the European Economic Area (EEA)	NeoRecormon®
Marketing authorization procedure	Concertation procedure, first approved in Germany 14 February 1990, followed by Central procedure (EMEA-H-C-116), approved 16 July 1997
Brief description of the product including:	Chemical Class Recombinant human erythropoietin (rHuEPO)
	Summary of mode of action Erythropoietin (EPO) is a glycoprotein that, as a growth factor, 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 uraemic rats, polycythaemic mice, dogs). After administration of epoetin beta, the number of erythrocytes, the hemoglobin (Hb) values and reticulocyte counts increase as well as the 59Fe incorporation rate. Erythropoietin is a growth factor that primarily stimulates red cell production. Erythropoietin receptors may be expressed on the surface of a variety of tumor cells.
	Important information about its composition Epoetin beta is produced by recombinant DNA technology in Chinese Hamster ovary cell line. Epoetin beta is identical in its amino acid and carbohydrate composition to erythropoietin that has been isolated from the urine of anemic patients.
Hyperlink to the Product Information	SmPC
Indication(s) in the EEA	Current: • Treatment of symptomatic anemia associated

	with chronic renal failure (CRF) in adult and pediatric patients. • Prevention of anemia of prematurity in infants with a birth weight of 750 to 1500g and a gestational age of less than 34 weeks • Treatment of symptomatic anemia in adult patients with non-myeloid malignancies receiving chemotherapy. • Increasing the yield of autologous blood from patients in a pre-donation programme. Its use in this indication must be balanced against the reported increased risk of thromboembolic events. Treatment should only be given to patients with moderate anemia (Hb 10 –13 g/dl [6.21–8.07 mmol/l], no iron deficiency) if blood conserving procedures are not available or insufficient when the scheduled major elective surgery requires a large volume of blood (4 or more units of blood for females or 5 or more units for males).
	Proposed: Not applicable

Dosage in the EEA	Current: **Treatment of symptomatic anemia in adult and pediatric chronic renal failure patients** Anemia symptoms and sequelae may vary with age, gender, and overall burden of disease; a physician's evaluation of the individual patient's clinical course and condition is necessary. NeoRecormon should be administered either subcutaneously or intravenously in order to increase haemoglobin to not greater than 12 g/dl (7.5 mmol/l). Due to intra-patient variability, occasional individual hemoglobin values for a patient above and below the desired hemoglobin level may be observed. Hemoglobin variability should be addressed through dose management, with consideration for the hemoglobin target range of 10 g/dl (6.2 mmol/l) to 12 g/dl (7.5 mmol/l). A sustained hemoglobin level of greater than 12 g/dl (7.5 mmol/l) should be avoided; guidance for appropriate dose adjustment for when hemoglobin values exceeding 12 g/dl (7.5 mmol/l) are observed are described in the EU SmPC section 4.2 Patients should be monitored closely to ensure that the lowest approved effective dose of NeoRecormon® is used to provide adequate control of the symptoms of anemia whilst maintaining a haemoglobin concentration below or at 12g/dl (7.45 mmol/l). Treatment with NeoRecormon® is divided into two stages: 1. **Correction phase** • Subcutaneous administration: – The initial dosage is 3 x 20 IU/kg body weight per week. The dosage may be increased every 4 weeks by 3 x 20 IU/kg and week if the increase of 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. For both routes of administration, the maximum dose should not exceed 720 IU/kg per week. 2. **Maintenance phase** To maintain an Hb 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 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. Treatment with NeoRecormon® is normally a long-term therapy. It can, however, be interrupted, if necessary, at any time. **Treatment of symptomatic chemotherapy-induced anemia in cancer patients:** NeoRecormon® should be administered by the subcutaneous route to patients with anemia (e.g. hemoglobin concentration ≤ 10g/dl (6.2 mmol/l)). Anemia symptoms and sequelae may vary with age, gender, and overall burden of disease; a physician's evaluation of the individual patient's clinical course and condition is necessary. 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). Due to intra-patient variability, occasional individual hemoglobin values for a patient above and below the desired hemoglobin level may be observed. Hemoglobin variability should be addressed through dose management, with consideration for the hemoglobin target range of 10 g/dl (6.2 mmol/l) to 12 g/dl (7.5 mmol/l). A sustained hemoglobin level of greater than 12 g/dl (7.5 mmol/l) should be avoided; guidance for appropriate dose adjustment for when hemoglobin values exceeding 12 g/dl (7.5 mmol/l) are observed are described in the EU SmPC section 4.2. 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. Appropriate dose titration should be considered. Patients should be monitored closely to ensure that the lowest approved dose of NeoRecormon® is used to provide adequate control of the symptoms of anemia. **Prevention of anemia of prematurity:** The solution is administered subcutaneously at a dose of 3 x 250 IU/kg b.w. per week. Premature infants who have already been transfused by the start of treatment with NeoRecormon® are not likely to benefit as much as untransfused infants. The recommended treatment duration is 6 weeks. **Treatment for increasing the amount of autologous blood:** The 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 Packed cell volume (PCV) allows blood donation, i.e. PCV ≥ 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. 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 red cell reserve = blood volume [ml] × (PCV - 33) ÷100 Women: blood volume [ml] = 41 [ml/kg] × body weight [kg] +1200 [ml]

	Men: blood volume [ml] = 44 [ml/kg] × body weight [kg] + 1600 [ml] 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 graphs illustrated in the EU SmPC section 4.2; Posology and method of Administration 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. 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 graphs presented in the EU SmPC section 4.2.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	<u>Current</u>: Epoetin beta is available as solution for injection [pre-filled syringes (PFS)] for intravenous (IV) and subcutaneous (SC) injections. Solution for injection in pre-filled syringe 500 IU, 2,000 IU, 3,000 IU, 4,000 IU, 5,000 IU, 6,000 IU, 10,000 IU, 20,000 IU and 30,000 IU
	Proposed: Not applicable
Is or will the product be subject to additional monitoring in the EU?	No

CRF = chronic renal failure; EPO = Erythropoietin; Hb = hemoglobin; IV = intravenous; rHuEPO = recombinant human erythropoietin; PCV = packed cell volume; PFS = pre-filled syringes and SC = subcutaneous.

GLOSSARY OF ABBREVIATIONS

Abbreviation	Definition
AEAB	Anti-Erythropoietin Antibody
amPRCA	Antibody-Mediated Pure Red Cell Aplasia
AOP	Anemia of prematurity
aOR	Adjusted Odds Ratio
anti-ESA	Anti-Erythropoiesis-Stimulating Agent
b.w.	body weight
CI	Confidence Interval
CIA	Chemotherapy induced anemia
CKD	Chronic Kidney Disease
CRF	Chronic Renal Failure
CV	Cardiovascular
CVD	Cardiovascular disease
DCC	Delayed cord clamping
DD	Dialysis-dependent
DOPPS	Dialysis Outcomes and Practice Patterns Study
ECAS	European Cancer Anemia Survey
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EPO	Erythropoietin
EPO-R	Erythropoietin Receptor
ESA	Erythropoietin Stimulating Agent
ESRD	end stage renal disease
EU	European Union
GA	Gestational age
Hb	hemoglobin
HIF	Hypoxia-inducible factor
HSA	human serum albumin
HR	Hazard Ratio
ICC	Immediate cord clamping
IV	intravenous
IBD	International Birth Date
IMP	Investigational Medicinal Product
IU	International Unit
MAH	Marketing Authorization Holder

Abbreviation	Definition
NDD	Non-dialysis dependent
PABD	pre-operative autologous blood donation
PCR	polymerase chain reaction
PCV	Packed Cell Volume
PFS	Pre-filled Syringe
pmp	per million population
PRCA	Pure Red Cell Aplasia
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
PY	Patients Years
QoL	Quality of Life
RBC	Red Blood Cell
rhuEPO	Recombinant Human Erythropoietin
RMP	Risk Management Plan
RT/chemo	Radiotherapy and Cisplatin Chemotherapy
RT-PCR	Reverse transcription polymerase chain reaction
RRT	Renal Replacement Therapy
SC	subcutaneous
SmPC	Summary of Product Characteristics
TEEs	Thromboembolic Events
THA	Total Hip Arthroplasty
TKA	Total Knee Arthroplasty
UK	United Kingdom
US	United States
USRDS	United States Renal Data System

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 ANEMIA ASSOCIATED WITH ADULT CHRONIC KIDNEY DISEASE

- **Incidence and Prevalence**

Anemia is a common complication of chronic kidney disease (CKD) due to erythropoietin (EPO) deficiency as well as decreased red blood cell survival, increased blood loss, impaired absorption of dietary iron, iron deficiency, inflammation, and decreased utilization of iron stores (Babitt and Lin 2012; Kovesdy et al. 2022). According to the World Health Organization (WHO), anemia is defined as a serum hemoglobin (Hb) level of <12 g/dL in women and <13 g/dL in men. A recent study in Sweden reported an incidence rate of 9.0 per 100 patient years (PY) for any anemia and 3.0 per 100 PY for severe anemia for 45,637 adult patients with non-dialysis dependent (NDD)-CKD (stages III-V). A total of 26% of the CKD patients developed anemia and 10.4% experienced severe anemia (Hb) <10 g/dL) (Xu et al. 2023). The incidence of severe anemia of CKD in North Denmark showed a similar trend with an incidence rate of 3.0 per 100 PY and observed proportion of 42.3% (Vestergaard et al. 2020). In Spain, France and Italy, the respective incidences reported for anemia in CKD were 10.9%, 10.9% and 11.4% (Cases et al. 2023; Dardim et al. 2023; Minutolo et al. 2023). In dialysis–dependent (DD)-CKD patients, the incidence of anemia was high and varied between 56.4% and 69.7% from 2015 to 2017(Cases et al. 2023).

The prevalence of anemia was 34% in Spain in CKD stage IIIa-V and increased to 71.8-73.4% in stage V NDD-CKD patients while a high prevalence of 91.0% was reported in DD-CKD patients, from 2015 to 2017 (Cases et al. 2023). The estimated prevalence of anemia of CKD in NDD-CKD patients France was 43.6% to 44.9% respectively between 2015 and 2017. (Dardim et al. 2023). A real–world study in Italy conducted on 101,143 individuals with NDD-CKD (IIIa-V) reported 39.6% of patients with anemia at baseline. The prevalence of anemia (adjusted for age and sex) was 33.8% among NDD-CKD patients in Italy and increased with CKD stage, with values ranging from 28.2% to 78.9% in 2016 (Minutolo et al. 2023). In the United States (US), the National Health and Nutrition Examination Survey estimated the prevalence of 25.3% for anemia in CKD patients between 1999 to 2018 with an increasing prevalence as CKD stage progressed from 17.1% in stage IIIa to 66.1% in stage V (Kovesdy et al. 2022). In pre-dialysis CKD patients with an estimated glomerular filtration rate below 60 ml/min, the reported prevalence of anemia and severe anemia was 55.9% and 14.9%, respectively in Turkey from February to August 2018. (Alagoz et al. 2020).

The incidence and prevalence of anemia in CKD is presented in Table 2.

Table 2 Incidence and prevalence of anemia in CKD

Anemia in adult CKD patients				
Country	**Population (Stage)**	**Incidence rate (per 100 PY) or Incidence proportion (%)**	**Prevalence (%)**	**Reference**
Sweden	NDD-CKD (III-V)	IR (*any anemia): 9.0 per 100 PY IR (#severe anemia): 3.0 per 100 PY Incidence proportion *Any anemia: 26.0% #Severe anemia: 10.4%	NR	Xu et al, 2023
North Denmark	CKD (IIIa-V)	IR (#severe anemia): 3.0 per 100 PY Incidence proportion: 42.3%	NR	Vestergaard et al, 2020
Spain	NDD-CKD (IIIa-V) DD-CKD	Incidence proportion NDD: 10.9% DD: 56.4-69.7%	NDD: 34.0% DD: 91.0%	Cases et al, 2023
France	NDD-CKD (all stages)	Incidence proportion: 10.9%	44.9%	Dardim et al, 2023
Italy	NDD-CKD (IIIa-V)	Incidence proportion: 11.4%	33.8%	Minutolo et al, 2023
US	CKD (IIIa-V)	NR	Anemia: 25.3% #Severe anemia: 1.9%	Kovesdy et al, 2022
Turkey	NDD-CKD (III-V)	NR	Anemia: 55.9% #Severe anemia: 14.9%	Alagoz et al, 2020

CKD = Chronic kidney disease; dL = deciliter; g: gram; IR = ; Incidence rate; NDD = Non-dialysis dependent; NR = not reported; DD = Dialysis dependent; PY = Person years;
*Any anemia: Hb <12 g/L for females or <13 g/dL for males
#Severe anemia: Hb <10 g/dL

- **Demographics**

Age, gender and ethnicity: Patients aged 75 years and above, females, black individuals, those with CKD stage IIIb or higher, and individuals with concomitant diabetes or cardiovascular disease have a substantially increased likelihood of experiencing renal anemia (Kovesdy et al, 2022; Dardim et al. 2023). The presence of anemia related to CKD in dialysis patients displayed an association with age, suggesting a greater likelihood as patients progressed in age (Evans et al. 2020; Eriksson et al. 2016; Cases et al. 2023). The occurrence of age-related renal anemia in patients who had not yet initiated dialysis exhibited a similar pattern to that observed in anemia associated with CKD patients undergoing dialysis (Lamerato et al. 2022; Dardim et al. 2023; Xu et al. 2023).

- **Natural History of the Indicated Condition in the (Untreated) Population**

Mortality: Patients with CKD have a higher risk of serious CVD; therefore, the all-cause mortality is estimated to be much higher in these patients than in the general population. The United States Renal Data System (USRDS) (USRDS 2004) reported an estimated overall mortality rate of 209 per 1,000 patient exposure years (PY) for the dialysis population. Similarly, the Hemodialysis study (HEMO) revealed an overall mortality rate of 166 per 1000 PYs in new patients starting renal replacement therapy (Tsakiris et al. 1999). In contrast, the overall death rate in the US general population of 50 to 70 year olds ranges from 0.5 to 28 cases per 1,000 PYs. A European study of hemodialysis patients revealed a 1-year death rate of 14.2% in France, 17.8% in Germany, 15.4% in Italy, 14.7% in Spain, and 19.8% in the UK (Rayner et al. 2004). In CKD patients, anemia has been shown to be strongly associated with acute hospitalization for any cause [Hazard ratio (HR) 1.74; 95% confidence interval (CI) (1.57−1.93)] and with all-cause death [HR 1.82; 95% CI (1.70-1.94)] (Toft et al, 2020). A retrospective real-world study in Italy also reported an increased risk of death in CKD patients with anemia [HR: 2.24; 95% CI: 2.17-2.31) compared to patients without anemia (Minutolo et al. 2023). A systematic literature review on impact of renal anemia on patients from 2002-2018 reported pooled mean (95% CI) HRs for the risk of all-cause mortality in patients with CKD not on dialysis with Hb< 10 g/ dL and 10–12 g/dL were 1.70 (1.42-2.01) and 0.97 (0.92-1.01), respectively. The estimated HRs of all-cause mortality in patients with CKD on dialysis with Hb< 10 g/dL, 10-12 g/dL, and >12 g/dL were HR:1.56; 95% CI (1.4-1.7), HR: 1.17; 95% CI (1.09-1.26), and HR: 0.91; 95% CI (0.87-0.96), respectively (Palaka et al. 2020).

- **Risk factors for the disease**

Several risk factors are associated with an increased likelihood of developing anemia in CKD patients. Individuals aged 75 years and older had 2.1 times higher odds of anemia compared to those aged 18-44 years [OR:2.1; 95% CI (1.12-3.969)]. Additionally, multivariate logistic regression analyses reported higher odds of anemia development in females [(vs males; OR:1.7; 95% CI (1.33-2.21)], non-Hispanic Blacks [(vs non-Hispanic whites; OR:3.114 (2.3-4.14)] and participants with stage IIIb-V CKD [(vs stage IIIa CKD;

OR: 10.8 (3.5-33.4)]. Individuals with diabetes had 1.53 times higher odds of developing anemia compared to non-diabetic individuals [(OR:1.53; 95% CI (1.23-1.9)] (Kovesdy et al. 2022). A systematic review and meta-analysis on CKD patients conducted till February 2020 reported that females had 36% more risk of development of anemia than males with adjusted odds ratio [(aOR):1.36; 95% CI (1.1-1.7)] adjusted to age, sex, stage of disease and co-morbidities. Those over 50 years of age were 62% more likely to develop anemia compared to those less than 50 years old, although this association was not statistically significant [OR:1.6 95% CI (0.7-3.8)]. Moreover, Stage V CKD patients were found to be 13 times more likely to develop anemia than patients with stage I CKD [aOR:13.7; 95% CI (5.2-35.9)]. The meta-analysis also revealed that patients with comorbidities were nearly 3 times more likely to develop anemia than those with no evidence of comorbidities [aOR: 2.9; 95% CI (1.7-5.0). Also, the patients with BMI $\geq$ 30 kg/m2 were 49% less likely to develop anemia compared with patients whose BMI was between 18.5 and 25 kg/m^2 [aOR: 0.51; 95% CI: 0.3-0.9) (Shiferaw et al. 2020)..

- **Main Existing Treatment Options**

The principal aims of anemia management are to alleviate signs and symptoms arising from anemia, improve quality of life and to reduce the need for blood or red blood cell (RBC) transfusions. Treatment with Erythropoiesis-stimulating agents (ESAs), rather than transfusion, is a major element in the supportive care of patients with advanced CKD, of whom the vast majority suffer from anemia and its clinical consequences. Published guidelines on the management of anemia in patients with CKD include ESA therapy in the standard treatment of anemia of CKD [Padhi et al 2015, KDIGO 2012 and Locatelli et al. 2013].

KDIGO guidelines [KDIGO2012] recommend for adult CKD patients on dialysis that ESA therapy could be used to avoid having the Hb concentration fall below 9 g/dL by starting ESA therapy when the Hb level is between 9 – 10 g/dL. The European Renal Best Practice position statement suggests for the European population that Hb values should not be allowed to routinely fall below 10 g/dL in CKD patients. In high-risk patients, treatment initiation with ESA should be started at Hb values between 9 – 10 g/dL, in order to maintain an Hb value of approximately 10 g/dL during maintenance therapy [Locatelli et al.2013].

Individualization of therapy is considered a reasonable approach as some patients may have improvements in quality of life (QoL) at higher Hb concentrations and ESA therapy may be started above 10 g/dL.

In addition to epoetin beta other ESAs are available for clinical use: epoetin alfa, the biosimilar forms of epoetin alfa (including epoetin zeta), epoetin beta, epoetin theta, as well as darbepoetin alfa and methoxy polyethylene glycol-epoetin beta. Approved dosing schedules for ESAs include 3 to 7 injections per week as well as administration once every week and once every 2 weeks for treatment of anemia in renal patients.

Darbepoetin alfa can also be administered at bi-weekly or once-monthly intervals for correction of anemia in pre-dialysis patients, and methoxy polyethylene glycol-epoetin beta bi-weekly or once-monthly for anemia correction and maintenance treatment.

More recently, a new class of orally administered compounds has become available to stimulate erythropoiesis in renal anemia patients, i.e., the hypoxia-inducible factor (HIF) stabilizers, also known as inhibitors of prolyl hydroxylase domain inhibitors enzymes, which are small-molecule agents to treat renal anemia. Roxadustat was the first HIF stabilizer to get regulatory approval, and has been approved by regulatory authorities in China (2018), Japan (2020) and Europe (2021) for the treatment of renal anemia. Since then, other HIF stabilizers have become available: daprodustat, molidustat, vadadustat. Results from the global clinical development program of the HIF stabilizers published so far demonstrate non-inferiority compared to ESAs for efficacy in terms of Hb control, and mostly non-inferiority in CV safety with the exception of vadadustat, which did not meet non-inferiority criteria for CV safety compared to darbepoetin in non-dialysis patients. The main comparative advantage of HIF stabilizers is oral therapy and avoidance of injectable for patients that prefer an oral option.

- **Important co-morbidities**

An observational study from the Swedish Renal Registry evaluating the epidemiology and treatment patterns of anemia identified diabetes, cancer, cerebrovascular diseases, heart failure, myocardial infarction, and peripheral vascular disease as common comorbidities across Stages IIIb-V in ND and DD-CKD patients (Evans et al, 2020). A multi-national descriptive cross-sectional study conducted using data from Adelphi CKD Disease-Specific Programme (DSP) from June to September 2012 in France, Germany, Italy, Spain, and the UK reported hypertension, secondary hyperparathyroidism, Type 2 diabetes and dyslipidemia as common comorbidities in both dialysis and non-dialysis CKD patients (Eriksson et al. 2016). A study in Spain also revealed arterial hypertension, dyslipidemia, diabetes mellitus, and cardiovascular disease to be the most prevalent comorbidities in CKD patients (Cases et al. 2023).

SI.2 ANEMIA IN ADULT PATIENTS WITH NON-MYELOID MALIGNANCIES RECEIVING CHEMOTHERAPY (CHEMOTHERAPY INDUCED ANEMIA)

- **Incidence and Prevalence**

Anemia is recognized as a common problem in cancer patients and is prevalent in 30% to 90% of patients [Rodgers et al.2018]. Anemia is particularly prevalent in cancer patients receiving chemotherapy and/or radiation with mild to moderate anemia occurring in 40 to 70% of the patients.

The frequency and severity of anemia in cancer varies as per the type of cancer, definition of anemia and treatment involved. A systematic review of literature published

in 1966 through February 2003 identified the prevalence of anemia in specific cancers and assessed the impact of anemia on survival and quality of life. The prevalence of anemia in non-myeloid cancers ranged from 32%-93%, if the anemia cut off was taken as Hb level 90.0–110.0 g/L (Knight et al. 2004). In the US, a total of 7266 patients diagnosed with breast, colorectal, gastric, lung, and ovarian cancers who received chemotherapy between 2000 and 2012 were identified from database at Kaiser Permanente Southern California Health Plan. The study reported 3638 moderate to severe anemia episodes (Hb <10 g/dL) and 708 severe anemia episodes (Hb <8 g/dL) accounting for 38.2% cases of moderate and 7.4% severe cases of anemia among the cancer patients (Xu et al. 2016). In an observational, cross-sectional study from 21 Spanish hospitals between May 19 and May 23, 2008 on 214 patients with non-myeloid cancers [breast (37.6%), gastrointestinal (23.6%) and lung cancer (19.7%)] receiving chemotherapy, 48.1% had anemia (of whom 13% had levels <10 g/dL and 31% were symptomatic) (Steegmann et al. 2013). In Italy and Austria, an observational, cross-sectional study was conducted at clinics between November 2010 and March 2011 on 1412 patients with non-myeloid tumors (colorectal, breast, lung, prostrate, non-Hodgkin's disease, and other hematological cancers) A total of 809 patients (57%) had received three or fewer cycles of chemotherapy, and 477 (34%) received platinum-containing regimens. The overall prevalence of anemia was 32%, 196 patients (14%) were deemed anemic based on Hb concentrations $\leq$ 10 g/dL, 131 (9%) were deemed anemic based on anemia treatment data, and 121 (9%) based on the physician's diagnosis of anemia (Merlini et al. 2013). A real-world study on non-myeloid tumor patients in China treated with mecapegfilgrastim (a medication administered after chemotherapy cycles), reported anemia in 13 patients as an adverse drug reaction, with an incidence of 2.1% (Ma et al. 2021).

- **Demographics**

Anemia is more frequently observed in women, patients with solid tumors compared with haematological malignancies and in patients treated with chemotherapy. No associations were identified between anemia and age, stage, or tumor type of non-myeloid patients (Steegmann et al. 2013).

- **Natural History of the Indicated Condition in the (Untreated) Population**

Anemia may negatively affect the efficacy of cancer treatment and the patients' QoL. Thus, anemia in cancer may lead to lower tumor tissue oxygenation which is associated with a reduction in the sensitivity of tumors to radiation and some forms of chemotherapy. Anemia has been linked to an increased rate of tumor recurrence and may contribute to the progression of cancer and reduce survival rates [Calabrich et al.2011]. Anemia is associated with fatigue and results indicate that compared with cancer patients without anemia, those with anemia have a greater symptom burden, lower functional status and decreased QoL.

A systematic review of literature published in 1966 through February 2003 assessed the impact of anemia on survival and quality of life in cancer patients. The review reported an increased morbidity and mortality due to anemia. As anemia compromises the effectiveness of radiation therapy in at least some forms of cancer, an effect on mortality may be expected in patients treated with this modality (Knight et al. 2004).

- **The main existing treatment options**

Erythropoietin stimulating agents are included in treatment guidelines for chemotherapy-induced anemia in oncology. Cancer- and Chemotherapy- Induced Anemia, 2017 National Comprehensive Cancer Network (NCCN) guidelines recommend that, for patients undergoing palliative treatment, ESA therapy, blood transfusion or participation in a clinical trial can be considered depending on patient preferences [Rodgers et al.2018]. The panel recognized that whether a chemotherapy regimen is considered curative is not always clear. Under these circumstances, given that no other cause of anemia has been identified, the order of priority for anemia management should be consideration of RBC transfusion, clinical trial enrollment if available, followed by consideration of ESAs. When ESA use is decided upon, physicians are advised to use the lowest dose necessary to avoid transfusion.

Table 3 Epidemiology of chemotherapy related anemia

Indication/ target Population	**Treatment of symptomatic anemia in cancer patients receiving chemotherapy**
Prevalence	According to cancer type (Merlini et al. 2013): Breast: 23% Lung: 30% Prostate: 36% Colorectal: 21% Other tumor: 41% Non-Hodgkin's lymphoma: 36% Other haematological: 36%
Incidence	Percentage who were anemic at least once during the study according to cancer type (Merlini et al. 2013): Breast: 71% Lung: 83% Gastrointestinal/ colorectal: 62% Head/ neck: 72% Gynaecological: 88% Lymphoma/ myeloma: 80% Leukaemia: 74% Urogenital: 72% Other: 70%

- **Risk Factors of Diseases**

One of the major risk factors associated with anemia in adult patients with non-myeloid malignancies is chemotherapy causing chemotherapy induced anemia (CIA). Anemia at baseline prior to initiation of chemotherapy is also found to be associated with an increased incidence of CIA. Other risk factors predictive of CIA include response to iron treatment, advanced age, presence of metastases, the degree of Hb decrease within the first month of treatment, as well as tumor type and treatment duration (Bryer and Henry 2018).

- **Natural history of the indicated condition in the (untreated) population**

Mortality: The presence of anemia is associated with an increased risk of mortality. Mortality rates in anemic cancer patients depend on the tumor type, tumor stage and concomitant chemotherapy. Caro et al. (2001) systematically reviewed 60 papers reporting the survival of cancer patients according to hemoglobin levels and/ or presence of anemia. They found that patients with chemotherapy related anemia had a 65% increase in mortality risk compared with non-anemic chemotherapy patients (95% CI: 54-77%). Specifically, anemic patients with lung (19%; 95% CI: 10-29%), head and neck (75%; 95% CI: 37-123%), prostate (47%; 21-78%), and lymphoma (67%; 95% CI: 30-113%) cancer had an increased risk of death compared with non-anemic patients.

- **Important co-morbidities**

Anemic patients with non-myeloid cancers can have one or more comorbid conditions. A multicenter, prospective, observational study enrolled 154 patients at 18 sites in the US September 2014 to 31 October 2015. A total of 41 (27.9%) patients presented with comorbidity which included chronic pulmonary disease (15%), congestive heart failure or coronary heart disease (6.1%), cerebral vascular disease (1.4%) and others (Granfortuna et al. 2018). A retrospective study using Kaiser Permanente Southern California Health Plan database reported cerebrovascular disease, chronic obstructive pulmonary disease/emphysema, diabetes, liver/peptic ulcer disease, renal disease, and vascular disease as some of the comorbidities present in the patients with anemia and non-myeloid malignancy (Xu et al. 2016).

SI.3 ANEMIA OF PREMATURITY IN INFANTS WITH A BIRTH WEIGHT OF 750 TO 1,500G AND A GESTATIONAL AGE (GA) OF LESS THAN 34 WEEKS

- **Incidence and Prevalence**

Low birth weight infants, including premature infants, are especially susceptible to developing iron deficiency anemia because they have smaller iron stores at birth and a greater iron requirement concurrent with a rapid increase in the red cell mass than term infants (Long, 2012). Furthermore, increased haemolysis, shortened red blood cell lifespan, low circulating EPO levels, blood sampling, and blood loss associated with medical procedures may also contribute to anemia.

To our knowledge, there are a lack of epidemiological studies investigating the incidence and prevalence of anemia in infants with a birth weight of 750 to 1,500 g and a gestational age (GA) of less than 34 weeks. In a cohort of 310 Brazilian infants with a birth weight of less than 1500 g and GA of less than 34 weeks, the prevalence of anemia at one year of corrected age was 26.5% (95% CI: 21.8-31.6%) and of iron deficiency was 48% (95% CI: 39.0-56.9%) (Ferri et al, 2014). Also, anemia of prematurity (AOP) has been reported in premature infants with birth weight range between 186 g to 2160 g and GA before 37 weeks (Li et al. 2021; Kitaoka et al. 2023).

A comprehensive systematic review and meta-analysis of randomized controlled trials (RCTs) published from inception until 30 September 2020, evaluated the effects of immediate cord clamping (ICC) and delayed cord clamping (DCC) in preterm infants. A total of four RCTs were included for analysis. The studies included infants born before the completion of the 37th week of gestation with birth weight ranged between 186 g to 2160 g. Out of the included 543 infants, 276 underwent ICC while 267 underwent DCC. Anemia of prematurity events were reported in 166 infants with an incidence of 30.6% (Li et al. 2021). In Japan, preterm infants born with a median GA of 34.4 weeks (range 33.3-35.3 weeks) and an average birth weight of 1993±397 g reported anemia of prematurity in 158 infants with an incidence of 44.1% (Kitaoka et al. 2023)

- **Demographics**

Studies indicate that infants born prematurely, before completing the 37th week of gestation and with birth weights ranging between 186 g and 2160 g, are susceptible to anemia of prematurity (Li et al. 2021; Kitaoka et al. 2023).

- **Natural History of the Indicated Condition in the (Untreated) Population**

No evidence was retrieved pertaining to natural history in literature sources for anemia associated with AOP in infants.

- **Risks Factors of the Disease**

Various risk factors have been considered for the development of AOP. Lower GA [(OR 0.19 ; 95% CI (0.11- 0.32)], small for gestational age (SGA ; 7.17, 2.15- 23.9), low maternal Hb level before birth [(OR 0.66; 95% CI (0.49- 0.87)], low Hb at birth [(OR 0.71; 95% CI (0.57- 0.89)], and multiple large blood samplings [(OR 1.79; 95% CI (1.40- 2.29)] showed significantly higher odds for AOP development (Kitaoka et al. 2023).

- **Main Existing Treatment Options**

The treatment of anemia in premature infants involves considering their unique hematological transition, comorbidities associated with preterm birth, illness severity, and iatrogenic factors. Neonates born prematurely, especially those with a birth weight under 1500 g or GA less than 32 weeks, are at high risk of requiring one or more packed red blood cell transfusions. In fact, up to 80% of extremely preterm infants and 50% of preterm infants may require transfusions. Extremely low birth weight infants often

receive their first transfusion within the first 2 weeks of life, with 80% requiring additional transfusions throughout their hospitalization (Chaudhary et al. 2022; Alan and Arsan 2015).

Additional treatment options are preventive strategies for anemia of prematurity to start life with higher Hb, which include ESAs. ESA treatment has been studied as an alternative to transfusions in preterm infants, and trials reported varying degrees of success attributed to differences in dose and timing when ESAs were administered, and enrollment of larger and healthier preterm infants at low risk for transfusion. A Cochrane analysis (was conducted to assess the effectiveness and safety of ESAs (initiated early before eight days after birth) compared with placebo or no intervention in reducing blood transfusions and other parameters in preterm and/or low birth weight infants. The review included 34 studies enrolling 3643 infants, all analyses compared ESAs versus a control consisting of placebo or no treatment. The authors concluded that early administration of ESAs reduced the use of red blood cell transfusions, the volume of RBCs transfused, and donor exposure after study entry. Small reductions were likely to be of limited clinical importance, and donor exposure probably was not avoided, given that all but one study included infants who had received RBC transfusions before trial entry.

- **Important co-morbidities**

No evidence was retrieved in literature sources pertaining to co-morbidities for anemia associated with AOP in infants

SI. 4 POST-ELECTIVE SURGERY ANEMIA REQUIRING TREATMENT / BLOOD TRANSFUSION

- **Incidence and Prevalence**

No data was available for increasing the yield of autologous blood from patients in a pre-donation programme. Anemia is common in surgical patients. In over 1.2 million adults who underwent elective total hip arthroplasty (THA) or total knee arthroplasty (TKA), approximately 15.4% developed postoperative blood loss anemia without transfusion, while 1.1% developed anemia and received a transfusion (Liu et al. 2023). In Germany, the incidence of postoperative anemia in patients undergoing elective surgery across various operative disciplines was estimated to be 49.2% (Kunz et al. 2020).

- **Demographics**
- Post-operative anemic patients were older and majority were of Black ethnicity (Liu et al. 2023). **Natural History of the Indicated Condition in the (Untreated) Population**
- No data was available regarding mortality of post-operative anemic patients. **Risks Factors of Diseases**

Postoperative anemia occurs frequently for surgical patients. Duration of hospitalization, [(OR 1.186; 95% CI (1.083-1.1.299)], postoperative delirium [(OR 3.949; 95% CI (1.358-

11.480) are significantly associated with postoperative anemia in patients undergoing elective surgery (Kunz et al. 2020).

- **Main Existing Treatment Options**
- Anemia is a common condition among surgical patients and has been associated with worse clinical outcomes. Recommendations from the International Consensus Conference on Anemia Management in Surgical Patients advises preoperative screening for anemia to accurately diagnose its cause and initiate appropriate therapy before surgery. In cases of iron deficiency anemia, intravenous (IV) iron is generally preferred over oral supplementation. Combined therapy with ESA and IV iron is recommended for the patients with non-pure iron deficiency anemia, which might effectively reduce the need for RBC cell transfusion. Red blood cell transfusion may be considered for severe, symptomatic postoperative anemia where clinical need cannot be met by volume replacement or hematinic medication alone (Shander et al. 2023). For patients undergoing cardiac surgery, anemia treatment should include ESA in combination with low-dose IV iron to stimulate erythropoiesis and increase Hb levels. Anemia treatment with ESA generally can be divided into 2 different regimens. First, short-term intervention with 200 to 500 U/kg ESA for 1-to-3 days in combination with or without iron substitution; and second, long-term interventions with 100-to-150 U/kg once to twice per week over 2-to-4 weeks in combination with iron substitution. Additionally, subcutaneous vitamin B12 or oral folic acid supplementation is also recommended (Kloeser et al. 2023).
- **Important comorbidities**

A study in US analyzed adults who underwent primary elective THA or TKA from January 2015 to December 2020. Common comorbidities in anemic patients with or without transfusion in both THA and TKA were acute kidney injury, diabetes mellitus, chronic obstructive pulmonary disease, obesity, hypothyroidism, hypertension, and depression. Patients with acute blood loss anemia who received a transfusion were at increased risk for developing pulmonary embolism [(aOR 1.83; 95% CI (1.34-2.51)], and venous thromboembolism [(aOR 1.39; 95% CI (1.14-1.70)] following THA (Liu et al. 2023).

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

1. MYELOFIBROSIS

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 body weight (b.w.) administered daily either subcutaneously (SC) or intravenously (IV), with the exception of fibrotic changes of the bone marrow which occurred if the packed cell volume (PCV) values exceeded 80%. A further study in dogs revealed that the myelofibrosis does not occur if the PCV is kept below 60 %. The observation of myelofibrosis is therefore irrelevant to the clinical situation in man as a PCV exceeding 80% (corresponding to a hemoglobin value of approx. 27 g/dL) is not reached in clinical practice.

Relevance to human usage: No

Discussion: Not relevant to human usage as PCV of 80% is not reached in clinical practice.

2. REPRODUCTION 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.

Relevance to human usage: No

Discussion: No indication for effects on reproductive system.

3. CARCINOGENICITY

The risk of NeoRecormon® to promote tumor progression has been addressed by a number of non-clinical studies presented in the initial registration dossier and its subsequent amendments (Rebel, Boehringer Mannheim Report No. AZ212, 1995).

During these studies no effect of NeoRecormon® was observed on the proliferation of non-hematological normal or malignant cells in vitro or transplantable tumors in vivo.

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

In order to address the potential risk of NeoRecormon® as a growth factor causing proliferation or modified differentiation of tumor tissue in patients, the following in vitro and in-vivo studies were conducted:

- Investigation of the carcinogenic potential of murine erythropoietin during long term administration in mice.
- Detection of EPO receptor mRNA (by polymerase chain reaction [PCR]) in human cell lines and in human tissue cultures of solid and hematological tumors.
- Proliferative behavior of tumor cells during administration of NeoRecormon®, including EPO receptor regulation and signal transduction.
- Effect of NeoRecormon® on the growth of human skin cells and of tumor cells
- Pathophysiology and effect of NeoRecormon® in tumor-associated anemia

Update since submission of the original dossier:

Since submission of the initial registration dossier for NeoRecormon® there is growing evidence suggesting that erythropoietin in addition to its stimulatory activity for erythroid induction and differentiation is a pleiotropic cytokine with other important biological functions. The question of tumor growth in response to treatment with ESAs was subject of numerous publications. As for all growth factors there are theoretical concerns that these compounds could act as a growth factor in various tumor types expressing the EPO-R. However, there is substantial heterogeneity in these published data which complicate the direct comparison of results. While EPO-R mRNA can be detected by sensitive reverse transcription polymerase chain reaction (RT-PCR) methods in many cell types or tissue samples, it has been suggested that the presence of EPO-R mRNA is not necessarily predictive of surface expression of functional EPO-R in human tumor cells (Sinclair et al. 2008; Laugsch et al. 2008). The localization of EPO-R in various tissues has been demonstrated by using mainly one particular anti-EPO-R antibody, which has now been characterized to have immunoreactivity against other proteins in addition to EPO-R and therefore has limited utility for immunological EPO-R detection and is especially not suitable for immunohistochemistry on tissues (Elliott et al. 2006). Data published with this antibody has therefore to be considered non-conclusive.

Recently published non-clinical data on erythropoietin-induced stimulation of tumor cell proliferation are contradictory, partly due to the different applied methodologies used and no clear conclusion about the clinical relevance can be drawn. Of note, in the studies which suggested potential growth promoting effects, supra-therapeutic doses were used (Nowrousian 2002).

Relevance to human usage: Yes

Discussion: Erythropoietins are growth factors, and as with other growth factors, there is a hypothetical concern that epoetin beta could act as growth factor for human tumor types. However, up to date no respective evidence has been observed in preclinical or clinical studies with epoetin beta.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Cumulative patient exposure is presented for Roche-sponsored interventional clinical trials conducted with epoetin beta as the Investigational Drug (or as the comparator in Roche sponsored trials for Mircera) since 17 March 1997 until 13 February 2014.

The main development program studies for filing activities were completed by 2006, and although there have been some Phase IV or specific investigator lead studies since that time the exposure numbers do not change considerably.

The estimated cumulative exposure to epoetin beta, placebo, and comparator drugs in Roche-sponsored interventional clinical trials is presented in Table 4. Since

17 March 1997, an estimated total of 5,389 patients have received epoetin beta via clinical trial participation.

Table 4 Cumulative Patient Exposure to Epoetin beta in Roche Sponsored Interventional Trials since 17 March 1997

Treatment Arm	Roche-Sponsored Interventional Studies
Epoetin beta	5,389
Placebo	698
Comparator	2,412
Total	**8,499**

Table 5 presents cumulative exposure by demography for Roche-sponsored interventional clinical trials conducted with epoetin beta as the primary IMP.

Table 5 Cumulative Summary of Patient Demographics in Roche-Sponsored Interventional Trials (all indications)

Age Range	Number of subjects
< 18 years	149
≥ 18 and ≤ 65 years	2345
> 65 years	1287
Unknown	1608
Total	**5,389**
Sex	**Number of subjects**
Female	2,264
Male	2,022
Unknown	1,103
Total	**5,389**
Race	**Number of subjects**
American Indian or Alaska Native	0
Asian	199
Black or African American	38
Multiple	2
Native Hawaiian or Other Pacific Islander	0
Other	24
White	2,295
Unknown	2,831
Total	**5,389**

Table 6 Cumulative Summary of Patient Demographics in Roche-Sponsored Interventional Trials – Split by Treatment Indication

	Indication		
	Renal Anemia	Chemotherapy induced anemia	Other
Age Range	**Number of subjects**		
< 18 years	0	1	148
≥ 18 and ≤ 65 years	793	1216	336
> 65 years	534	720	33
Unknown	1208	400	0
Total	**2535**	**2337**	**517**
Sex	**Number of subjects**		
Female	827	1172	265
Male	931	839	252
Unknown	777	326	0
Total	2535	2337	517
Race	**Number of subjects**		
Asian	34	163	2
Black or African American	28	5	5
Multiple	0	0	2
Other	13	6	5
White	1064	959	272
Unknown	1396	1204	231
Total	**2535**	**2337**	**517**

Combined Safety Databases

Roche have created large clinical trial safety databases for both the renal anemia and oncology indications by combining per-patient data from all available randomized, controlled clinical trials. These databases have been used for extensive evaluations of the safety of NeoRecormon®, including estimates of events of interest presented in Part II of this document. In both indications this has involved including, where possible, data from older Boehringer-Mannheim sponsored studies. The restriction to include randomized, controlled studies only, as the most appropriate for the evaluation of risk, in some of the databases result in in difference in patient exposure numbers.

Oncology: The clinical trial safety database is best characterized by the 12 controlled clinical trials with NeoRecormon® conducted in cancer patients since granting of the Marketing Authorisation, including some studies sponsored by the previous Marketing Authorization Holder (MAH) Boehringer-Mannheim. These trials have been summarized in the updated meta-analysis on the effects of NeoRecormon® in cancer patients (Fourth

meta-analysis report 2007) Table 7 to Table 10 refer to this population including 2301 patients.

Renal Anemia: In the renal anemia setting the largest combined database includes 16 randomised control trials with NeoRecormon®, including studies sponsored by Boehringer Mannheim , and Roche-sponsored studies where NeoRecormon® was the comparator Table 8 refers to this population of 4,214 patients.

Table 7 Duration of exposure (Oncology)

Durations of Exposure	Persons (N=1244)	Person Years
At least one day	1,244	322.6
At least 4 weeks	1,091	n/a
At least 16 weeks	399	n/a
Median duration	85.0 d	n/a
Minimum duration	1 d	n/a
Maximum duration	461d	n/a

d = days; N = number

Table 8 Duration of exposure (Renal Anemia)

	NeoRecormon (N=2464)	All Other ESA's (N=1750)
	PEY	PEY
Overall Exposure	3,046.12	1,423.61

ESA = Erythropoietin Stimulating Agent; N = number; PEY = Person Years

Table 9 By Dose (Oncology)

Dose of Exposure	Persons (N=1244)	Person Years
Cumulative Dose ≤10'000 IU	105	9.1
At least 4 weeks	41	n/a
At least 16 weeks	1	n/a
Median duration	22.0 d	n/a
Minimum duration	1 d	n/a
Maximum duration	369 d	n/a
Cumulative Dose 10'000 – 30'000 IU	372	57.4
At least 4 weeks	283	n/a
At least 16 weeks	28	n/a
Median duration	56.0 d	n/a
Minimum duration	5 d	n/a
Maximum duration	217 d	n/a
Cumulative Dose >30'000 IU	767	256
At least 4 weeks	767	n/a
At least 16 weeks	370	n/a
Median duration	111.0 d	n/a
Minimum duration	35 d	n/a
Maximum duration	461 d	n/a
Once weekly regimen	231	89.0
At least 4 weeks	215	n/a
At least 16 weeks	176	n/a
Median duration	162.0 d	n/a
Minimum duration	1 d	n/a
Maximum duration	369 d	n/a
More than once weekly regimen	1013	233.5
At least 4 weeks	876	n/a
At least 16 weeks	223	n/a
Median duration	75.0 d	n/a
Minimum duration	1 d	n/a
Maximum duration	461 d	n/a

d = days; IU= International Unit; N = number; n/a=not applicable.

Exposure by dose information was not available for the renal anemia setting in this format.

Table 10 Special Population Exposure (Oncology)

	Persons	Person Years
Pregnant Women	x	x
Lactating Women	x	x
Solid Tumors	779	205.0
Hematological Tumors	461	116.5
Patients on chemo- or radiotherapy	1164	320.3
Patients not on chemo- or radiotherapy	80	2.3
Hepatic impairment	xx	xx
Cardiac impairment	xxx	xx
Sub Populations with Genetic Polymorphisms	Not Studied	

x Pregnant and Lactating women were not included in the studies.

xx Hepatic impairment was not an exclusion criteria from the clinical studies, however no specific sub-group analysis on patients with hepatic impairment was conducted.

xxx Cardiac impairment was not an exclusion criteria from the clinical studies, however no specific sub-analysis on patients with cardiac impairment was conducted.

Exposure by dose information was not available for the renal anemia setting in this format.

Special Population Exposure (Renal Anemia)

The main special population of interest in the renal anemia indication was the pediatric population as detailed below.

Table 11 Pediatric Population Studies (Renal Anemia)

Study No.	Children with	N	Design	(Initial) Epoetin beta dose	Duration
MF3904	Hematocrit ≤ 28 % ≤ 3 transfusions last 6 months or ferritin ≥ 700ng/ml, hemodialysis or peritoneal dialysis	**149**	OS	40 or 80 or 100 IU /Kg bw x3/week or 300 IU/Kg bw x1/week, all IV	26 months actual treatment: mean 335 days, range 6 – 803 days
MF4323	End-stage renal failure	**60**	OS	maintenance SC: dose adjusted for hematocrit	12 weeks actual treatment: mean 81 days, range 29-99 days

IU = international unit; IV =intravenous; O =open label; S =single group; SC= subcutaneous.

Prevention of Anemia of Prematurity

The efficacy of epoetin beta has been demonstrated in a series of controlled studies with around 500 infants receiving active treatment. Benefits in transfusion reduction / avoidance have been established with a dose of 250 IU/kg/TIW and a typical treatment duration of 6 weeks, designed to continue therapy until the point in time that the natural decline in hemoglobin following birth is anticipated to reverse. Whilst a positive risk benefit has been established for this treatment approach, it cannot be assumed to also apply to shorter treatment durations where the efficacy maybe compromised.

As these studies were conducted over twenty years ago by the previous MAH for epoetin beta (Boehringer Mannheim), Roche does not have access to individual patient data.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

Table 12 Important Exclusion Criteria in Pivotal Studies in the Development Program

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Hypersensitivity	Contraindication	No	Hypersensitivity is a rare occurrence. Patients with known hypersensitivity should not be treated with NeoRecormon®. If hypersensitivity occurs, treatment with epoetin beta must be discontinued. (Hypersensitivity to the active substance or to any of the excipients is included in the EU SmPC, in Section 4.3).
Poorly controlled hypertension	Contraindication	No	Blood pressure should be adequately controlled in all patients before, at initiation of, and during treatment with epoetin beta. If high blood pressure is difficult to control by medical treatment or dietary measures, the dose must be reduced or administration discontinued. ('Uncontrolled hypertension' is included in the EU SmPC, in Section 4.3)
Epilepsy	Previous experience with other ESAs has led to a general precaution on their use in patients with epileptic seizures	No	Caution should be used in patients with epilepsy in section 2.4 of the CDS. There has been no evidence that epoetin beta caused epilepsy in real life use.
Severe renal insufficiency with creatinine >2.5mg/dL (>220mol/L)	Used exclusively in oncology studies to avoid alternative aetiologies of anemia.	No	Extensive experience shows NeoRecormon® to be safe in patients with renal failure. This exclusion criterion was not based on safety concerns.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Acute bleeding, chronic inflammatory disease, haemolytic anemia (e.g. haptoglobin <50 mg/dL)	Patients excluded due to presence of other risk factors for aneamia other than malignancy or CKD which might confound response to epoetin beta and interpretation of studies. The presence of chronic inflammatory disease is common in CKD and blunts epoetin responsiveness.	No	Exclusion from trials not based on safety concerns. No additional risks of clinical significance is expected in this population.
Thrombocytopenia: platelet count <$20x10^9$/L at baseline	In oncological studies, to reduce risk of severely ill subjects not completing study compliantly	No	No specific hazard seen in these subjects, outside of a clinical trial they could receive epoetin beta, if their treating physician believed it would be beneficial. This exclusion criterion was not based on safety concerns.
Thrombocytosis: platelet count >$450x10^9$/L at baseline	Previous experience with other ESAs has led to a general precaution on their use in patients with thrombocytosis	No	Use of epoetin beta should be interrupted if platelets rise above upper normal level, according to Warnings and Precautions. Caution should be used in this population in section 2.4 of the CDS. Use of epoetin beta should be interrupted if platelets rise above upper normal level, according to Warnings and Precautions. No additional risks of clinical significance is expected in this population..

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Serious disorder of the coagulation system	A potential confounder of response and compliance within clinical trials	No	Whilst some effects on Thromboembolic Events (TEE) have been suggested for ESAs these are in subjects with multiple pathologies and risk factors. Epoetin beta should be used with caution in patients with high or low clotting but their benefit from treatment may still outweigh potential risks. This exclusion criterion was not based on safety concerns.
Serious disorder of the central nervous system	A potential confounder of response, compliance and assessment within clinical trials	No	Whilst some effects on Thromboembolic Events (TEE) have been suggested for ESAs these are in subjects with multiple pathologies and risk factors. Epoetin beta should be used with caution in patients with high or low clotting but their benefit from treatment may still outweigh potential risks. This exclusion criterion was not based on safety concerns.
Vitamin B12 deficiency Folic acid deficiency	Potential impact on the assessment of the efficacy of epoetin beta. Patients excluded due to presence of other risk factors for anemia other than malignancy or CKD.	No	Deficiencies of folic acid or vitamin B12 reduce the effectiveness of ESAs and should therefore be corrected. Failure to respond to epoetin beta therapy should prompt a search for causative factors - see Section 4.4 in the EU SmPC. This exclusion criterion was not based on safety concerns.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Pregnant and lactating women	The safety and efficacy of ESAs have not been established in pregnant or breast-feeding women.	No	Caution should be exercised when prescribing to pregnant women. It is unknown whether epoetin beta is excreted in human breast milk. A decision on whether to continue or discontinue breastfeeding or to continue or discontinue therapy with epoetin beta should be made taking into account the benefit of breast-feeding to the child and the benefit of epoetin beta therapy to the women, see sections 2.5.1 – 2.5.3 in the CDS.

CKD = chronic kidney disease; ESA = Erythropoietin Stimulating Agent; E.U = European Union; SmPC = Summary of Product Characteristics; TEE = thromboembolic events

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

The clinical trial development program for NeoRecormon® was unable to detect certain types of adverse drug reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Use in Pregnancy and Lactation

No clinical studies in pregnant women have been conducted up to date. No non-interventional studies, including registries, were designed and conducted to obtain information in this population. Hence, the length of exposure in pregnant women cannot be currently estimated. Cumulative summary of pregnancy data presented in Annex 7.

Table 13 Exposure of special populations included or not in clinical trial development program

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	Not included in the clinical development program
Patients with relevant comorbidities:	
Patients with hepatic impairment	Hepatic impairment was not an exclusion criteria from the clinical studies, however no specific sub-group analysis on patients with hepatic impairment was conducted.
Patients with renal impairment	In the majority of the studies conducted in cancer patients, severe renal insufficiency with creatinine above 2.5 mg/dL was used as an exclusion criterion. Therefore, there is no experience in patient with renal failure and cancer. However, NeoRecormon® is indicated for the treatment of anemic patients with chronic kidney disease including patients receiving dialysis or in predialysis. In these patients the serum creatinine is usually above 2.5 mg/dL.
Patients with cardiovascular impairment	Cardiac impairment was not an exclusion criteria from the clinical studies, however no specific sub-analysis on patients with cardiac impairment was conducted.
Immunocompromised patients	Not included in the clinical development program
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	Refer to Table 6. Patients of various ethnic origins were enrolled in clinical trials with NeoRecormon®
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program
Pediatric Patients	Refer to Table 11 - Pediatric Population in Renal Anemia
Elderly Patients	1,184 patients aged over 65 years were exposed to NeoRecormon® (cutoff date 13 February 2014)
Special Population Exposure (Oncology):	
Patients with Solid Tumors	Refer to Table 10
Patients with Hematological Tumors	Refer to Table 10
Patients on chemo- or radiotherapy	Refer to Table 10
Patients not on chemo- or radiotherapy	Refer to Table 10

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORISATION EXPOSURE

SV.1.1 Method used to calculate exposure

The number of patients exposed to epoetin beta is estimated based on internal logistics and finance data, i.e. ex-factory shipments to Roche customers and licensing partners. The data from the MAH in South Korea – "JW Pharmaceuticals" is included in the total.

Roche has acquired epoetin beta from Boehringer Ingelheim in late 1997. Thus, the cumulative exposure is available from 1998 onwards. The data is available at monthly intervals hence the annual report includes records from 1 February until 31 January of the following year. It is assumed that 10% of 10,000 IU pre-filled syringe (PFS) presentations and 100% of 20,000 and 30,000 presentations are used in oncology. All other presentations are assumed to be used for renal anemia patients.

Defined daily doses and treatment duration vary according to indication (60 – 1,600 IU/kg body weight), in this report 468,000 IU/patient/year equivalent have been used to calculate the number of oncology anemia patients and 324,480 for renal anemia patients.

SV.1.2 Exposure

The estimated exposure to epoetin beta via commercial supply for the interval 1 January 1998 to 31 January 2023 amounts to approximately 6.28 million patients-years.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

In the 1970s autologous and homologous transfusions addressed as blood doping were misused to enhance physical performance. In addition, the potential misuse of ESAs to enhance athletic performance (especially in endurance sports because of the expected increase in aerobic performance as a result of increasing hemoglobin levels) has been known since the 1980s. Hematocrit can reach dangerous levels. In addition, lack of medical supervision and fluid loss during endurance can increase the risk of serious adverse events associated with increase in viscosity due to misuse. Roche is collaborating with WADA (World Antidoping Association) to prevent misuse for doping purposes.

The issue is addressed in the SmPC in section 4.4 Special warnings and precautions for use.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

Not applicable.

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

No new safety concerns have been identified since EU RMP was last submitted, however, some previous safety concerns have been reclassified and removed from the list of safety concerns in line with the new definitions of important identified risks, important potential risks and missing information introduced in the [Good Pharmacovigilance Practice – Revision 2] GVP-V(R2), as follows:

- **"Thromboembolic Events (TEE), (Chemotherapy induced anemia)"** which was previously classified as an important identified risk is no longer presented in the EU RMP.

Reasons for changes (reclassification/removal) to the list of safety concerns:

It no longer meets the definition of important safety concern (i.e., it does not require additional pharmacovigilance [PV] activities or additional risk minimization activities or

routine risk minimization activities recommending specific clinical measures to address the risk).

- **"Hypertension including hypertensive crisis and associated symptoms, (Renal Anemia, Chemotherapy induced anemia)"** which was previously classified as an important identified risk is no longer presented in the EU RMP.

Reasons for changes (reclassification/removal) to the list of safety concerns:

It no longer meets the definition of important safety concern (i.e., it does not require additional PV activities or additional risk minimization activities or routine risk minimization activities recommending specific clinical measures to address the risk).

- **"Disease progression and overall survival (Chemotherapy induced anemia)"** which was previously classified as an important potential risk is no longer presented in the EU RMP.

Reasons for changes (reclassification/removal) to the list of safety concerns:

It no longer meets the definition of important safety concern (i.e., it does not require additional PV activities or additional risk minimization activities or routine risk minimization activities recommending specific clinical measures to address the risk).

- **"Cardiovascular (CV) adverse events, (Renal Anemia)"** which was previously classified as an important potential risk is no longer presented in the EU RMP.

Reasons for changes (reclassification/removal) to the list of safety concerns:

It no longer meets the definition of important safety concern (i.e., it does not require additional PV activities or additional risk minimization activities or routine risk minimization activities recommending specific clinical measures to address the risk).

- **"CV complications due to excessive Hb increase in case of misuse by healthy persons (not related to any indication)"** which was previously classified as an important potential risk is no longer presented in the EU RMP.

Reasons for changes (reclassification/removal) to the list of safety concerns:

It no longer meets the definition of important safety concern (i.e., it does not require additional PV activities or additional risk minimization activities or routine risk minimization activities recommending specific clinical measures to address the risk).

- **"Thromboembolic Events (TEE) (Renal Anemia, Increasing the Yield of Autologous Blood from Patients in a Pre–Donation Program)"** which was previously classified as an important potential risk is no longer presented in the EU RMP.

Reasons for changes (reclassification/removal) to the list of safety concerns:

It no longer meets the definition of important safety concern (i.e., it does not require additional PV activities or additional risk minimization activities or routine risk minimization activities recommending specific clinical measures to address the risk).

- **"Retinopathy of Prematurity (Anemia of Prematurity)"** which was previously classified as an important potential risk is no longer presented in the EU RMP.

Reasons for changes (reclassification/removal) to the list of safety concerns:

It no longer meets the definition of important safety concern (i.e., it does not require additional PV activities or additional risk minimization activities or routine risk minimization activities recommending specific clinical measures to address the risk).

- **"Infantile Hemangioma (Anemia of Prematurity)"** which was previously classified as an important potential risk is no longer presented in the EU RMP.

Reasons for changes (reclassification/removal) to the list of safety concerns:

It no longer meets the definition of important safety concern (i.e., it does not require additional PV activities or additional risk minimization activities or routine risk minimization activities recommending specific clinical measures to address the risk).

- **"Pediatric Population (Chemotherapy induced anemia)"** which was previously classified as missing information is no longer presented in the EU RMP.

Reasons for changes (reclassification/removal) to the list of safety concerns:

In the indication chemotherapy induced anemia, this patient group is excluded from use as per Section 4.1 of the current EU SmPC.

- **"Pregnancy and Lactation (Chemotherapy induced anemia, Renal Anemia, Increasing the Yield of Autologous Blood from Patients in a Pre–Donation Program)"** which was previously classified as missing information is no longer presented in the EU RMP.

Reasons for changes (reclassification/removal) to the list of safety concerns:

There is no scientific evidence to expect a different safety profile in pregnant/ lactating patients.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

SVII.3.1. Presentation of important identified risks and important potential risks

Information on important identified risks

ANTI-ERYTHROPOIETIN ANTIBODY MEDIATED PURE RED CELL APLASIA (RENAL ANEMIA)

MedDRA Terms:

Anti-Erythropoietin Antibody mediated Pure Red Cell Aplasia (AEAB-mediated PRCA) is defined based on specific diagnostic criteria (please see under “severity and nature of risk”).

The global safety database is automatically searched for all reports meeting defined search criteria (broad search for relevant terms and laboratory test results) to identify potential cases of PRCA. These reports are reviewed and assessed by a specifically trained safety scientist based on the above referenced diagnostic criteria.

Potential mechanisms:

AEAB-mediated PRCA is an autoimmune disease in which erythropoiesis is inhibited by antibodies specific for EPO. The reason an individual develops AEAB-mediated PRCA has been controversial and remains unclear in background cases, but is attributed to a breakdown of immune tolerance. This seems to have occurred more frequently with the human serum albumin (HAS)-free formulation of EPO alpha which may suggest a role for product stability in the sequence of events that can lead to breakdown of immune tolerance (Locatelli et al. 2007). The antibodies were described inhibiting EPO binding to its receptor and could block erythropoiesis in in vitro models (Schellkens and Jiskoot 2006). Patients with AEAB-mediated PRCA develop anti-EPO antibodies that neutralize any administered epoetin and also endogenous EPO leading to a deletion of erythroid precursor cells in the bone marrow (Boven et al. 2005).

Evidence source(s) and strength of evidence:

Isolated cases of confirmed AEAB-PRCA have been reported in association with different ESAs including NeoRecormon® during postmarketing experience. A surge in reports occurred between 1998 and 2003, primarily with epoetin alfa SC formulation, for reasons that remain uncertain.

Characterization of the risk:

- *Frequency with 95% CI:*

Spontaneous data from the Roche safety database reveal a reporting rate of 1.25 cases per 100,000 PY in renal anemia patients treated with NeoRecormon® by any route over the 33 years the product is marketed, which is provided by the MAH in the PBRER with DLP 13 February 2023.

- *Incidence/Prevalence:*

PRCA is an uncommon condition, but the true incidence is not known. PRCA may affect any age group, and affects men and women with the almost same frequency. It has been described in all part of the world, and there seems to be no ethnic or racial predisposition (Dessypris 2000). There are a few estimates of the incidence of PRCA in specific subgroup (e.g., patients with thymoma), but no studies describing the incidence or prevalence of PRCA in the indication populations were found in the literature.

The incidence of epoetin-induced PRCA was very low before 1998, but a sudden upsurge of reports of PRCA cases in patients with CKD was reported from 1999 to 2002. The majority of these were reported in patients treated subcutaneously with the HSA-free epoetin alfa formulation marketed outside the US (Rossert et al. 2004; Macdougall 2005). The number of global PRCA cases has declined since 2003, following increased awareness of the disorder and changes in the handling and administration of the of epoetin alfa (Macdougall 2005).

The approximate background rate ranges between 1 in 20,000 (PRISM/Eprex registry) to 1–2 in 100,000 PYs. A Dutch cohort study with 1677 dialysis patients on ESAs revealed 1 case of PRCA during the follow up, yielding an incidence rate of 29 in 100,000 with wide CI (95% CI 0.7–162 in 100,000), (Kharagjitsingh et al. 2005).

Despite the awareness of the medical community triggered by the initial publication by Casadevall in 2002 (Casadevall et al. 2002), no increased occurrence of AEAB-mediated PRCA subsequent to exclusive use of epoetin beta was found after annual analysis up to 14 February 2014, during the 12th year of close monitoring. The occurrence of AEAB-mediated PRCA remains stable (i.e., at 0.117 cases per 10,000 PY).

- *Severity:*

AEAB-mediated PRCA is much more severe than the anemia associated with CKD which induced ESA treatment and usually results in long-term dependence on transfusion which may or may not resolve spontaneously. The current definition of PRCA is specified by Casadevall et al. 2004 as follows: fall in RBC of about 1%/day, reticulocyte count below 1%, no major changes in white cell count, platelet count, or differential leukocyte count; normal cellularity of bone marrow, less than 1%

erythroblasts (occasionally up to 5% proerythroblasts or basophilic erythroblasts), normal myeloid cells and megakaryocytes). The decreases in laboratory parameters may be obscured in practice by lack of data (Casadevall et al. 2004). The following criteria according to N. Casadevall are used to define the AEAB-mediated PRCA: anemia with reticulocytopenia (< 5000/mm³), platelets and white blood cells normal, bone marrow with normal cellularity and absence of erythroblasts (< 5%). The working definition which is applied by the company for report verification is kept simple for practicality reasons.

- *Reversibility:*

There is a consensus that ESA should be discontinued in any patient with confirmed AEAB-mediated PRCA (Eckardt and Casadevall 2003). However, spontaneous remissions after cessation of ESAs are rare. Therefore, immunosuppressive therapy should be provided in most cases (Verhelst et al. 2004; Rossert et al. 2005). Moreover, patients must not be switched to another recombinant ESA because of class-reactivity of antibodies with endogenous and all recombinant ESA molecules (Casadevall et al. 2002; Weber et al. 2002).

- *Impact on quality of life:*

The clinical consequences of the deficiency of RBCs in AEAB-mediated PRCA comprise a steady decline in hemoglobin, elevated serum iron due to reduced incorporation and an increase in serum EPO due to reduced receptor-carrying RBCs and reduced receptor density. Reticulocytopenia occurs due to the block of erythropoiesis. Profound transfusion-dependent anemia develops, which could be lethal without appropriate treatment (Schellkens and Jiskoot 2006). Multiple repeat transfusions (as would be required if immunomodulatory therapy were unsuccessful) also have severe impact on quality of life, especially iron overload and need for chelation.

Risk factors and risk groups:

CKD patients who receive SC administration.

Preventability:

Erythropoiesis-Stimulating Agent should be discontinued in any patient with suspected PRCA and the patient investigated for the presence of antibodies (Eckardt and Casadevall 2003). Patients must not be switched to another recombinant ESA because of cross-reactivity of antibodies with endogenous EPO and all ESAs (Casadevall et al. 1996; Casadevall et al. 2002). Product handling with respect to reducing product exposure to ambient temperature is important. Chemical and physical in-use stability of the reconstituted solution has been demonstrated for one month at 2°C – 8°C. From a microbiological point of view, once opened, the reconstituted solution may be stored for maximum of one month at 2°C – 8°C. Other in-use storage times and conditions are the responsibility of the user.

See SmPC Section 6.4, Special precaution for 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”.

Impact on the benefit-risk balance of the product:

Due to the severity AEAB mediated PRCA is considered to be a key risk for NeoRecormon®. If adequately diagnosed and treated the condition is manageable and, given the benefits of significant improvement in hematological indices, patient quality of life (QoL), and the avoidance of transfusion the benefit-risk balance remains positive.

Public health impact:

Not understood as public health concern because of very rare occurrence.

Information on important potential risks

There are no important potential risks for NeoRecormon®.

SVII.3.2. Presentation of the Missing Information

There is no missing information for NeoRecormon® requiring further characterization.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 14 Summary of safety concerns

Summary of safety concerns	
Important identified risks	Anti-Erythropoietin Antibody mediated Pure Red Cell Aplasia (AEAB-mediated PRCA) (Renal Anemia)
Important potential risks	None
Missing information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- Specific adverse reaction follow-up for Anti-Erythropoietin Antibody mediated Pure Red Cell Aplasia (Renal Anemia).

Post-marketing active surveillance by a Guided Questionnaires (GQ) designed to better understand the risk factors for this condition (refer to Annex 4 for details).

Other forms of routine pharmacovigilance activities for safety concerns:
None.

The Roche standard pregnancy follow-up process was implemented for all products to request additional information on the medication history of the exposed parent, relevant medical history for the mother and father, previous obstetric history, the current pregnancy, fetal and infant conditions, and results of tests and investigations for any pregnancy complication or congenital abnormality during pregnancy or within the first year of the infant's life.

Cumulative data will be presented in Periodic Safety Update Reports (PSURs)/PBRERs.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 15 Monitoring program for AEAB-mediated PRCA

Program short name and title: Monitoring program for AEAB-mediated PRCA
Rationale and Program Objectives: The objective of this program is an early identification of AEAB-mediated PRCA cases.
Program design: Monitoring program for AEAB-mediated PRCA and the free offer for antibody testing in serum
Study populations: Patients exposed to NeoRecormon®
Milestones: Submission of Annual Report with EU PBRER Data cut off 14 February each year

AEAB = Anti-erythropoietin antibody; PRCA = pure red cell aplasia

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 16 On-going and planned additional pharmacovigilance activities

Study **Status**	**Summary of Objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Monitoring program for AEAB-mediated PRCA Ongoing	Early identification of AEAB-mediated PRCA cases	Anti-Erythropoietin Antibody mediated Pure Red Cell Aplasia (Renal Anemia)	Submission of Annual Reports with EU PBRER	Data cut off 14 February each year
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance				
None				

AEAB = Anti-erythropoietin antibody; PRCA = pure red cell aplasia

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are no planned or ongoing imposed post-authorization efficacy studies for NeoRecormon®.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

RISK MINIMIZATION PLAN

V.1 ROUTINE RISK MINIMIZATION MEASURES

Table 17 Description of Routine Risk Minimization Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Anti-Erythropoietin Antibody mediated Pure Red Cell Aplasia (AEAB-mediated PRCA) (Renal Anemia)	**Routine risk communication:** Warning about the risk of pure red cell aplasia in association with erythropoietin therapy is included in SmPC section 4.4 (Special warnings and precautions for use) and section 4.8 (Undesirable effects). Recommendation on storage conditions for pre-filled syringes and for multi-dose formulation is included in SmPC section 6.4 (Prevention by precaution on storage condition). **Routine risk minimization activities recommending specific clinical measures to address the risk:** In case PRCA is diagnosed, therapy with NeoRecormon® must be discontinued and patients should not be switched to another ESA. This warning is adequately described in the EU SmPC section 4.4 (Special warnings and precautions for use) **Other risk minimization measures beyond the Product Information:** • **Medicine's legal status**: NeoRecormon® is medicinal product subject to restricted medical prescription

AEAB = Anti-erythropoietin antibody; ESA = Erythropoietin Stimulating Agent; EU = European Union; PRCA = pure red cell aplasia; SmPC = Summary of Product Characteristics

V.2. ADDITIONAL RISK MINIMISATION MEASURES

Table 18 Additional Risk Minimisation Measures for AEAB-mediated PRCA

Additional Risk Minimisation Measure	Monitoring program for AEAB-mediated PRCA - component offering HCPs free antibody testing in cases of suspected antibody-mediated PRCA
Objectives	To enhance the early and correct diagnosis of PRCA in suspected cases
Rationale for the additional risk minimization activity	The activity is intended to facilitate the accurate and rapid diagnosis of antibody-mediated PRCA. Ultimately this will lead to improved management and outcome of individual patients, although the impact in terms of patient outcome cannot be measured directly or indirectly.
Target audience and planned distribution path	Healthcare professionals and patients
Plans for evaluating the effectiveness of the interventions and criteria for success	Potential cases of AEAB-mediated PRCA with test results if available are provided in the annual PRCA status update reports. In these reports, test results and clinical consequences are discussed in detail. Single case analysis in the PRCA status update reports should demonstrate early confirmation of the suspected diagnosis and initiation of appropriate treatment in patients with AEAB-mediated PRCA. In the case reports of AEAB-mediated PRCA attributed to epoetin beta so far, the diagnosis could be confirmed early by antibody testing.

AEAB = Anti-Erythropoietin Antibody; HCP= Health Care Professional; PRCA = Pure Red Cell Aplasia; SmPC = Summary of Product Characteristics.

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

Table 19 Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Anti-Erythropoietin Antibody mediated Pure Red Cell Aplasia (AEAB-mediated PRCA) (Renal Anemia)	**Routine risk minimization measures:** SmPC section 4.4 and 4.8 SmPC section 6.4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC section 4.4, where warning to discontinue NeoRecormon® therapy in case of PRCA is provided **Other risk minimization measures beyond the Product Information:** NeoRecormon®'s legal status **Additional risk minimization measures:** Offering HCPs free antibody testing in cases of suspected antibody-mediated PRCA	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Guided Questionnaire for Anti-Erythropoietin Antibody mediated Pure Red Cell Aplasia (Renal Anemia) **Additional pharmacovigilance activities:** Monitoring program for AEAB-mediated PRCA (Category 1)

AEAB = Anti-Erythropoietin Antibody; HCP= Health Care Professional; PRCA = Pure Red Cell Aplasia; SmPC = Summary of Product Characteristics

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PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR NEORECORMON (EPOETIN BETA)

This is a summary of the risk management plan (RMP) for NeoRecormon®. The RMP details important risks of NeoRecormon, ®how these risks can be minimized, and how more information will be obtained about NeoRecormon risks and uncertainties (missing information).

NeoRecormon® summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how NeoRecormon® should be used.

This summary of the RMP for NeoRecormon® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of NeoRecormon® RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

NeoRecormon® is authorized for

- Treatment of symptomatic anemia associated with chronic kidney disease in patients on dialysis.
- Treatment of symptomatic renal anemia in patients not yet undergoing dialysis.
- Prevention of anemia of prematurity in infants with a birth weight of 750 g to 1,500 g and a gestational age of less than 34 weeks.
- Treatment of symptomatic anemia in adult patients with non-myeloid malignancies receiving chemotherapy.
- Increasing the yield of autologous blood from patients in a pre-donation program. Its use in this indication must be balanced against the reported increased risk of thromboembolic events. Treatment should only be given to patients with moderate anemia (hemoglobin 10–13 g/dL [6.21–8.07 mmol/L]), no iron deficiency) if blood conserving procedures are not available or insufficient when the scheduled major elective surgery requires a large volume of blood (four or more units of blood for females or five or more units for males).

(see SmPC for the full indication). It contains epoetin beta as the active substance and it is given by intravenous (IV) and subcutaneous (SC.) injections.

Further information about the evaluation of NeoRecormon® benefits can be found in NeoRecormon® EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of NeoRecormon®, together with measures to minimize such risks and the proposed studies for learning more about NeoRecormon risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In the case of NeoRecormon®, these measures are supplemented with *additional risk minimization* measures mentioned under relevant risks, below.

In addition to these measures, information about adverse events is collected continuously and regularly analysed: including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A LIST OF IMPORTANT RISKS AND MISSING INFORMATION

Important risks of NeoRecormon® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of NeoRecormon®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Anti-Erythropoietin Antibody mediated Pure Red Cell Aplasia (AEAB-mediated PRCA) (Renal Anemia)
Important potential risks	None
Missing information	None

II.B SUMMARY OF IMPORTANT RISKS

Anti-Erythropoietin Antibody mediated Pure Red Cell Aplasia (AEAB-mediated PRCA) (Renal Anemia)	
Evidence for linking the risk to the medicine	Isolated cases of confirmed AEAB-PRCA have been reported in association with different ESAs including NeoRecormon® during post-marketing experience.
Risk factors and risk groups	CKD patients who receive SC administration
Risk minimization measures	**Routine risk minimization measures:** Warning about the risk of pure red cell aplasia in association with erythropoietin therapy is included in SmPC section 4.4 (Special warnings and precautions for use) and section 4.8 (Undesirable effects). Recommendation on storage conditions for pre-filled syringes and for multi-dose formulation is included in SmPC section 6.4 (Prevention by precaution on storage condition). In case PRCA is diagnosed, therapy with NeoRecormon must be discontinued and patients should not be switched to another ESA. This warning is adequately described in the EU SmPC section 4.4 (Special warnings and precautions for use) **Additional risk minimization measures:** Monitoring program for AEAB-mediated PRCA - component offering HCPs free antibody testing in cases of suspected antibody-mediated PRCA
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Monitoring program for AEAB-mediated PRCA (Category 1) See section II.C of this summary for an overview of the post-authorization development plan.

AEAB = Anti-erythropoietin antibody; CKD = Chronic Kidney Disease; ESA = Erythropoietin Stimulating Agent; OS = overall survival; PRCA = pure red cell aplasia; SC = subcutaneous

II.C POST-AUTHORISATION DEVELOPMENT PLAN

II.C.1 Studies which are conditions of the marketing authorisation

The following program is considered condition of the marketing authorization :

- Monitoring program for AEAB-mediated PRCA
- Purpose of the study: Early identification of AEAB-mediated PRCA cases

II.C.2 Other studies in post-authorization development plan

There are no other studies required for NeoRecormon®.

ANNEX 4:

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

MIRCERA® / NeoRecormon® - Guided Questionnaire for:

- **Anti-Erythropoietin Antibody Mediated Pure Red Cell Aplasia**
- **Inadequate Response to Epoetin Treatment**
- **Anemia Refractory to Epoetin Treatment**
- **Unexplained Loss of Effect of Epoetin Treatment**

AER:	
Site No:	
Local Case ID:	

Patient ID/Initials:	
Patient Gender:	❑ M ❑ F
Date of Birth (dd-mmm-yyyy):	

There have been very rare reports of anti-erythropoietin antibody mediated pure red cell aplasia in patients treated with epoetins including MIRCERA and NeoRecormon. By filling in this questionnaire, you will help us to understand more fully the risk factors for this condition.

Definition of PRCA (specified by Casadevall et al.)
Fall in hemoglobin of about 0.1 g/dL/day
Reticulocyte count below 10 or 20 x 10^9/L
No major changes in white cell count, platelet count, or differential leukocyte count
Normal cellularity of bone marrow, less than 1% erythroblasts (occasionally up to 5% with evidence of a maturation arrest), normal myeloid cells and megakaryocytes

Confirmatory investigations
Bone marrow aspirate: normal cellularity and < 5% erythroblasts, evidence of block of maturation
Serum: presence of anti-erythropoietin antibodies, evidence of their neutralizing capacity

Indication for Epoetin Treatment
Patient with anemia associated with chronic kidney disease
❑ not on dialysis ❑ on dialysis
Other indication (please specify):
HLA configuration of patient
❑ not done ❑ done
Specify:

Treatment with blood transfusions		
Date (dd/mmm/yy)	RBC Units	Reason for transfusion

Treatment with any type of epoetin since first treatment (co-medications to be captured in the SAE form)						
Epoetin (generic + Trade name)	Dose	Route	Start date (dd/mmm/yy)	Stop date (dd/mmm/yy)	Duration	Batch #

Laboratory data (specify the units). Other parameters (WBC, platelets, etc.) to be captured in the SAE form.						
Date (dd/mmm/yy)	Hemoglobin Unit:_____	Hematocrit %	MCV μm^3 or fL	Reticulocytes Unit:_____	Serum iron Unit:_____	Serum ferritin Unit:_____

Anti-erythropoietin antibody test		❑ **not done**	❑ **done**
Date (dd/mmm/yy)	Lab Name & Address (local or Roche lab)	Method (RIPA, bridged ELISA, etc.)	Results

Anti-MIRCERA antibody test		❑ **not done**	❑ **done**
Date (dd/mmm/yy)	Lab Name & Address (local or Roche lab)	Method (RIPA, bridged ELISA, etc.)	Results

Neutralization activity test		❑ not done	❑ done
Date (dd/mmm/yy)	Lab Name & Address (local or Roche lab)	Method (cell lines)	Results

Bone marrow examination		❑ not done	❑ done
Date (dd/mmm/yy)	Type	PRCA	Detailed Results (percentage of the different cell lines or send a copy of the original report)
	❑ Biopsy ❑ Aspirate	❑ Yes ❑ No ❑ Unknown	
	❑ Biopsy ❑ Aspirate	❑ Yes ❑ No ❑ Unknown	

Medical history or concomitant condition	Medical history or concomitant condition
Chronic blood loss (gut, uterus, other) ❑ Yes ❑ No ❑ Unknown Details:	Malnutrition ❑ Yes ❑ No ❑ Unknown Details:
Iron deficiency (absolute or functional) ❑ Yes ❑ No ❑ Unknown Details:	Access infection (dialysis patients) ❑ Yes ❑ No ❑ Unknown Details:
Vitamin B12 deficiency ❑ Yes ❑ No ❑ Unknown Details:	Surgical inflammation ❑ Yes ❑ No ❑ Unknown Details:
Folate deficiency ❑ Yes ❑ No ❑ Unknown Details:	Systemic Lupus Erythematosus ❑ Yes ❑ No ❑ Unknown Details:
Carnitine deficiency ❑ Yes ❑ No ❑ Unknown Details:	Juvenile/rheumatoid arthritis ❑ Yes ❑ No ❑ Unknown Details:
Chronic rejecting allograft ❑ Yes ❑ No ❑ Unknown Details:	Multiple endocrine gland insufficiency ❑ Yes ❑ No ❑ Unknown Details:
Viral hepatitis ❑ Yes ❑ No ❑ Unknown Details:	Aluminum toxicity ❑ Yes ❑ No ❑ Unknown Details:
B 19 Parvovirus infection ❑ Yes ❑ No ❑ Unknown Details:	Underdialysis ❑ Yes ❑ No ❑ Unknown Details:
Epstein-Barr infection ❑ Yes ❑ No ❑ Unknown Details:	Hemoglobinopathies (thalassemias, sickle cell anemia) ❑ Yes ❑ No ❑ Unknown Details:
Human T-lymphocyte virus (HTLV-1) ❑ Yes ❑ No ❑ Unknown Details:	Multiple myeloma, myelofibrosis ❑ Yes ❑ No ❑ Unknown Details:

Medical history or concomitant condition
HIV infection ❑ Yes ❑ No ❑ Unknown Details:
Other viral infections ❑ Yes ❑ No ❑ Unknown Details:
Tuberculosis ❑ Yes ❑ No ❑ Unknown Details:
Other infections/inflammation ❑ Yes ❑ No ❑ Unknown Details:

Medical history or concomitant condition
Other malignancy ❑ Yes ❑ No ❑ Unknown Details:
Hemolysis ❑ Yes ❑ No ❑ Unknown Details:
Other relevant conditions ❑ Yes ❑ No ❑ Unknown Details:

Concomitant medication

Medication	Yes	No	Unknown	Dose	Start date	Stop date
ACE Inhibitors	❑	❑	❑			
AT1 receptor antagonist therapy	❑	❑	❑			
Phenytoin	❑	❑	❑			
Azathioprine	❑	❑	❑			
Chloramphenicol	❑	❑	❑			
Procainamide	❑	❑	❑			
Isoniazid	❑	❑	❑			
Interferon	❑	❑	❑			
Other suspect drugs Specify:						

Other relevant information (clinical course, outcome, treatment of AE, etc.)
Specify:

Completed by:

Name: ..... Position: .....

Signature: ..... Date: .....

E-mail: .....

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES (if applicable)

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES (if applicable)

Monitoring program for AEAB-mediated PRCA:

The program offers free antibody testing to health care professionals in cases of suspected antibody-mediated Pure Red Cell Aplasia (PRCA).

The activity is intended to facilitate the accurate and rapid diagnosis of antibody-mediated PRCA. Ultimately this will lead to improved management and outcome of individual patients, although the impact in terms of patient outcome cannot be measured directly or indirectly.

Potential cases of AEAB-mediated PRCA with test results are provided in the annual PRCA status update reports. In these reports, test results and clinical consequences are discussed in detail in PART III.2.

The information received on AEAB-mediated PRCA during the review period for the PBRER 1120020 does not alter the risk profile of epoetin beta. No changes to current PV and risk minimization activities for epoetin beta are warranted at this time.