THE EU RISK MANAGEMENT PLAN FOR MIRCERA®/METHOXY POLYETHYLENE GLYCOL-EPOETIN BETA

RMP version to be assessed as part of this application: 13.1

RMP Version number: 13.1

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Date of final sign off: See latest date in date stamps on the last page of the document

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Rationale for submitting an updated RMP:

This risk management plan (RMP) version 13.1 is being updated in response to EMA/VR/0000309070 preliminary assessment report.

The RMP 13.0 was revised to discontinue free anti-Erythropoietin antibody testing (or re-testing) offered by Roche and remove all references associated with the testing. Mircera® has been on the market for >15 years and given the stable low incidence of anti-erythropoietin antibodies (AEAB)-mediated pure red cell aplasia (PRCA) associated with methoxy polyethylene glycol- epoetin beta over many years of monitoring coupled with no changes to the Mircera overall risk profile, it is considered appropriate to discontinue the free-testing offer while maintaining surveillance through regular safety reporting processes. Alternative testing options are available for healthcare professionals (HCPs) in hospitals and commercial labs and removing the provision of free antibody testing does not impact notification of the risk in the label nor the inclusion of PRCA testing protocols in other clinical guidelines.

Summary of significant changes in this RMP:

- Part 1: Product overview updated
- Annex 8 Updated with changes made in this RMP

Other RMP versions under evaluation:

RMP Version number: None

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Details of Currently Approved RMP:

RMP Version number: 12.3

Approved with Procedure Number: EMEA/H/C/000739/II/0068

Date of approval (opinion date): 31 October 2019

See last page for signature and date

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[redacted] Date

PART I: PRODUCT OVERVIEW

Active Substance(s) (INN or common name)	Methoxy polyethylene glycol-epoetin beta
Pharmacotherapeutic group(s) (ATC Code)	B03XA03
Marketing Authorization Holder(MAH) (or Applicant)	Roche Registration GmbH
Medicinal products to which this Risk Management Plan(RMP) refers	One
Invented name(s) in the European Economic Area (EEA)	Mircera®
Marketing authorization procedure	Centrally Approved Product
Brief description of the product including:	Chemical Class: Erythropoietin receptor activator
	Summary of mode of action: Methoxy polyethylene glycol-epoetin beta shows an activity at the receptor level characterized by a slower association to the receptor, a reduced specific activity in vitro with an increased activity in vivo, as well as an increased half-life when compared to erythropoietin.
	Important information about its composition: Protein produced by recombinant Deoxyribonucleic acid (DNA) technology in Chinese Hamster Ovary (CHO) cells and covalently conjugated to a linear methoxy-polyethylene glycol (PEG).
Hyperlink to the Product Information	Mircera Product Information
Indication(s) in the EEA	Current: Treatment of symptomatic anemia associated with chronic kidney disease in adult patients Treatment of symptomatic anaemia associated with chronic kidney disease (CKD) in paediatric patients from 3 months to less than 18 years of age who are converting from another erythropoiesis stimulating agent (ESA)

	after their haemoglobin level was stabilised with the previous ESA
	Proposed: Not applicable
Dosage in the EEA	Current: *Treatment of symptomatic anaemia in adult chronic kidney disease patients:* Administered either subcutaneously or intravenously in order to increase haemoglobin to not greater than 12 g/dl (7.45 mmol/l). *Adult patients not currently treated with an erythropoiesis stimulating agent (ESA):* The recommended starting dose in patients not on dialysis is 1.2 µg/kg body weight, administered once every month as a single subcutaneous injection to increase haemoglobin levels to greater than 10 g/dl (6.21 mmol/l). Alternatively, a starting dose of 0.6 µg/kg bodyweight may be administered once every two weeks as a single intravenous or subcutaneous injection in patients on dialysis or not on dialysis. *Adult patients currently treated with an ESA:* Patients currently treated with an ESA can be switched to MIRCERA® administered once a month as a single intravenous or subcutaneous injection. The starting dose of MIRCERA® is based on the calculated previous weekly dose of darbepoetin alfa or epoetin at the time of the substitution as described in the Mircera EU SmPC. The first injection should start at the next scheduled dose of the previously administered darbepoetin alfa or epoetin. *Paediatric patients from 3 months to less than 18 years of age currently treated with an ESA*: Paediatric patients whose haemoglobin level has been stabilised by treatment with an ESA can be converted to methoxy polyethylene

	glycol-epoetin beta administered once every 4 weeks as an IV or SC injection but keeping the same administration route. The starting dose of methoxy polyethylene glycol-epoetin beta is calculated based on the total weekly ESA dose at the time of conversion as described in the Mircera EU SmPC.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: 25 (Japan only), 30, 50, 75, 100, 120, 150, 200, 250 µg/0.3 ml solution for injection in pre-filled syringes. 360 µg /0.6 ml solution for injection in pre-filled syringes.
	Proposed: Not applicable
Is or will the product be subject to additional monitoring in the EU?	No

CHO=Chinese Hamster Ovary; DNA=Deoxyribonucleic acid; EEA = European Economic Area; ESA =erythropoiesis stimulating agent; EU SmPC = European Union Summary of Product Characteristics; INN = International nonproprietary name; MAH = Marketing Authorization Holder; PEG =polyethylene glycol; RMP=Risk Management Plan.

ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse drug reaction
AE	Adverse event
AEAB	Anti-erythropoietin antibody
ARISg	Adverse Reaction Information System Global
BP	Blood pressure
CDC	Centers for Disease Control
CHF	Congestive heart failure
CI	Confidence interval
CKD	Chronic kidney disease
CRP	C-reactive protein
CSR	Clinical Study Report
CVD	Cardiovascular disease
DLP	Data lock point
DOPPS	Dialysis Outcomes and Practice Patterns Study
DVT	Deep vein thrombosis
EEA	European Economic Area
EMEA	European Medicines Evaluation Agency, now known as EMA (European Medicines Agency)
EPO	Erythropoietin
EpoR	Erythropoietin receptor
ESA	Erythropoiesis stimulating agent
ESRD	End-stage renal disease
EPAR	European Public Assessment Report
EU	European Union
eGFR	Estimated Glomerular Filtration Rate
GI	Gastrointestinal
GFR	Glomerular Filtration Rate
Hb	Hemoglobin
HD	Hemodialysis
HEMO	Hemodialysis Study
IBD	International Birth Date
iDMC	independent Data Monitoring Committee

Abbreviation	Definition
IV	Intravenous
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
PAERI	Prevalence of Anemia in Early Renal Insufficiency
PEY	Patient exposure years
PK	Pharmacokinetics
PL	Package Leaflet
PMP	Per Million Population
PRAC	Pharmacovigilance Risk Assessment Committee
PBRER	Periodic Benefit-Risk Evaluation Report
PRCA	Pure red cell aplasia
PSUR	Periodic Safety Update report
PVD	Peripheral vascular disease
RBC	Red blood cell
RSI	Request for Supplementary Information
RMP	Risk Management Plan
rhuEPO	Recombinant human erythropoietin
RR	Relative risk
RRT	Renal replacement therapy
SAE	Serious Adverse Event
SC	Subcutaneous
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
UK	United Kingdom
USA	United States of America

PART II: SAFETY SPECIFICATION

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

SI.1 TREATMENT OF SYMPTOMATIC ANEMIA ASSOCIATED WITH CHRONIC KIDNEY DISEASE

INCIDENCE

In Europe, epidemiological data demonstrates a substantial burden of anemia in chronic kidney disease (CKD) patients, with incidence rate of 9.0 per 100 patient years (PY) for any anemia and 3.0 per 100 PY for severe anemia (in Sweden and Denmark) (Xu et al, 2023; Vestergaard et al. 2020). A single observational study from US found that among non-dialysis dependent CKD (NDD-CKD) patients (stages IIIa-V), the incidence rate increased from 7.4 per 100 PY after 1 year to 9.7 per 100 PY at 5 years of follow-up. The incidence of anemia in NDD-CKD population vary across different regions, ranging from 10.9% (in Spain and France) to 26.0% (in Sweden), while dialysis-dependent (DD-CKD) patients show markedly higher incidence of 56.4%-69.7% (in Spain) (Cases et al. 2023 ;Dardim et al. 2023 ; Xu et al, 2023).

PREVALENCE

The global burden of anemia attributable to CKD was 762.1 cases per 100,000 population in 2021, down from 841.2 cases per 100,000 population in 1990, according to the Global Burden of Disease 2021 database (Liu et al, 2025). Globally, the prevalence of anemia (any type) in (NDD-CKD ranged from 20.6% to 55.9% (Lamerato et al. 2022 ; Cases et al, 2023; Dardim et al. 2023; Awan et al. 2021; Alagoz et al, 2020) while the prevalence of moderate/ severe anemia ranged between 1% and 15% (Koyama et al. 2023; Kovesdy et al. 2023 ; Awan et al. 2021; Alagoz et al. 2020). A meta-analysis of 86 studies conducted across 10 Asian countries revealed that overall prevalence of anemia among all CKD stages was 42%. Analysis by disease stage revealed a clear progression in anemia prevalence with worsening kidney function: 23% in stage III CKD, 60% in stage IV CKD, and 80% in stage V CKD (Kim et al, 2025). In the US, studies have demonstrated that the prevalence of anemia in patients with NDD-CKD ranged from 20.6% to 25.3% (Alagoz et al. 2020; Kovesdy et al. 2023; Lamerato et al. 2022). Among these patients, the prevalence of moderate anemia (Hb <10.0 g/dL but >8.0 g/dL) to severe anemia (Hb <10 g/dL) ranged from 0.55% to 5.6%, with variation likely reflecting differences in study populations and CKD stages (Awan et al. 2021; Koyama et al. 2023 ; Kovesdy et al. 2023). In Europe, the prevalence of anemia ranged between 33.8%-55.9% in non-dialysis CKD patients (Minutolo et al. 2023; Dardim et al. 2023 ; Alagoz et al. 2020) while in dialysis-dependent (DD-CKD) patients disease burden is very high with anemia prevalence reaching 91.0% in Spanish cohorts Cases et al. 2023.

The incidence and prevalence of anemia in CKD is presented in Table 1

Table 1 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**
Asian countries (Meta-analysis)	CKD (I-V)	NR	All stages (pooled data): 42% Stage III: 23% Stage IV: 60% Stage V: 80%	Kim et al. 2025
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
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
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
Taiwan	CKD (all stages)	NR	9.2%	Chang et al. 2025
Turkey	NDD-CKD (III-V)	NR	Anemia: 55.9% #Severe anemia: 14.9%	Alagoz et al. 2020

Anemia in adult CKD patients				
Country	**Population (Stage)**	**Incidence rate (per 100 PY) or Incidence proportion (%)**	**Prevalence (%)**	**Reference**
US	NDD CKD (III-V)	NR	Anemia (all types): 20.6% $Moderate anemia: 3.6% #Severe anemia: 0.55%	Awan et al. 2021
US	NDD-CKD (IIIa-V)	IR (All types; after 1 year): 7.4 per 100 PY IR (All types; after 5 years): 9.7 per 100 PY	23%	Lamerato et al. 2022
US	CKD (IIIa-V)	NR	Anemia: 25.3% #Severe anemia: 1.9%	Kovesdy et al. 2023
US	CKD (III)	NR	#Moderate or severe anemia: 5.6%	Koyama et al. 2023
CKD: Chronic kidney disease; IR = incidence rate, NDD: Non-dialysis dependent; DD: Dialysis dependent; PY: Person years; NR = no result, g: gram; dL: deciliter *Any anemia: Hb <12 g/L for females or <13 g/dL for males #Severe anemia: Hb < 10 g/dL $Moderate anemia: Hb <10.0 g/dL but >8.0 g/dL				

DEMOGRAPHICS

The global burden of anemia attributable to CKD was higher in females (784.5 cases per 100,000) compared to males (748.1 cases per 100,000) according to the global burden disease (GBD) 2021 data (Liu et al. 2025). Severe anemia (Hb <10 g/dL) was more prevalent in women than in men across all estimated glomerular filtration rate (eGFR) (ml/min/1.73 m2) categories [eGFR 60-74:1.9% vs 1.3%; eGFR 45-79: 3.9% vs 3.1%; eGFR 30-44: 8.6% vs 7.5%; eGFR 15-29: 19.4% vs 14.4%; eGFR <15: 37.6% vs 29.7%] (Farrington et al. 2023). Patients aged 75 years and above, females, black individuals, those with CKD stage IIIB or higher, and individuals with concomitant diabetes and/orcardiovascular disease have a substantially increased likelihood of experiencing anemia (Kovesdy et al. 2023 ; 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). In elderly patients, the overall prevalence of anemia was

reported as 50.1% and prevalence increased with CKD disease severity (43.9% in stage III CKD, 64.0% in stage IV CKD and 72.8% in stage V CKD (St.Peter 2018).

THE MAIN EXISTING TREATMENT OPTIONS

Exogenous replacement of erythropoietin (EPO) by the recombinant protein hormone, epoetin, is a well-established therapy, widely replacing blood transfusion as treatment (Bernieh et al. 1995; Biesma et al. 1994; Lim et al. 1989; Ma et al. 1999; Macdougall 1998).

Treatment with erythropoietin 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 CKD (KDOQI Guidelines 2006, Revised European Best Practice Guidelines 2004; KDOQI Guidelines 2007; KDIGO Guidelines 2012; Locatelli et al. 2013).

In addition to methoxy polyethylene glycol-epoetin beta, other ESAs are available for clinical use: epoetin alfa, the biosimilar forms of epoetin alfa (including epoetin zeta), epoetin beta, epoetin theta and darbepoetin alfa. 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 once-monthly intervals for anemia in patients not on dialysis.

In patients with CKD, alleviation of anemia requires life-long treatment with an ESA. Most regimens for the treatment of anemia of CKD require one to three administrations of an ESA per week. Therefore, modifications extending the half-life of the protein to allow less frequent administration with sustained efficacy should improve the therapeutic utility and convenience of the drug. The pharmacological properties of methoxy polyethylene glycol-epoetin beta allow up to once-monthly dosing intervals, which is the recommended intravenous (IV) and subcutaneous (SC) dosing regimen for methoxy polyethylene glycol-epoetin beta.

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 prolyl hydroxylase inhibitors (commonly known as HIF stabilizers). In Europe, two HIF stabilizers are approved for the treatment of renal anemia, roxadustat and daprodustat. 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 HIFs is oral therapy and avoidance of injectables for patients that prefer an oral option.

RISK FACTORS FOR THE DISEASE

Several key risk factors significantly increase the likelihood of developing anemia in CKD patients. Advanced kidney disease severity plays a critical role, with patients in CKD stages IV-V being five times more likely to develop anemia compared to those in stages I-III [Pooled odds ratio (POR): 5.3; 95% CI (4.2–6.8)] (Taderegew et al, 2023). Furthermore, the patients with stage IIIb-V CKD have nearly 11 times higher odds of anemia compared to those with stage IIIa CKD [OR: 10.8 (3.5-33.4)] (Kovesdy et al, 2022).

Demographic factors also strongly influence anemia risk. Female CKD patients have higher odds of developing anemia than males [POR: 2.5; 95% CI (1.8–3.6)] (Taderegew et al, 2023; Kovesdy et al, 2022). Elderly patients aged 75 years and older have twice the risk compared to younger adults aged 18-44 years [OR: 2.1; 95% CI (1.12-3.969)] (Kovesdy et al, 2022). Race also plays a significant role, with non-Hispanic Blacks having three times higher odds compared to non-Hispanic whites [OR: 3.1; 95% CI (2.3-4.14)] (Kovesdy et al, 2022).

Comorbidities substantially impact anemia development. Stage of CKD (3–5) (pooled odds ratio (POR) = 5.33, 95% CI:4.20–6.76), CKD patients with diabetes mellitus have higher risk of developing anemia compared to those without diabetes [POR: 1.8; 95% CI (1.1-2.8)], while those with a history of hemodialysis are three times more likely to develop anemia [POR: 3.1; 95% CI (1.6–5.7)] (Taderegew et al, 2023). Overall, patients with comorbidities have nearly three times the risk compared to those without [adjusted odds ratio (aOR): 2.9; 95% CI (1.7-5.0)] (Shiferaw et al. 2020).

NATURAL HISTORY OF THE INDICATED CONDITION IN THE UNTREATED POPULATION

Compared to CKD patients without anemia, those with mild anemia showed increased risk for kidney failure or death [adjusted hazards ratio (aHR): 1.39; 95% CI (1.37-1.40)], while moderate/severe anemia demonstrated an even higher risk [aHR: 2.15; 95% CI (2.12-2.19)] (Koyama et al. 2023). A retrospective real-world study in Italy also reported an increased risk of death in non-dialysis-dependent CKD patients with anemia [HR: 2.24; 95% CI: 2.17-2.31) compared to patients without anemia (Minutolo et al. 2023).

IMPORTANT CO-MORBIDITIES:

Across multiple studies, CKD patients with anemia consistently demonstrate a high burden of comorbidities. In Taiwan, a retrospective study found that hypertension (69.2%) was the most prevalent comorbidity among CKD patients with anemia, followed by diabetes mellitus (41.4%), ischemic heart disease (31.2%), dyslipidemia (24%), cancer (24%), and stroke (20.8%) (Chang et al. 2025). Similarly, a large US study examining severe anemia in CKD patients identified heart failure (9.3%) and cancer (9.2%) as the most common serious comorbidities, with additional significant conditions including COPD (7.2%), cardiac dysrhythmia (7.1%), diabetes (7%), coronary artery disease (6.4%), depression (6.3%), and hypertension (5.7%) (Koyama et al. 2023)

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

1.1 SAFETY CONCERNS FROM NON-CLINICAL STUDIES / EXAGGERATED ERYTHROPOIESIS

1.1.1 Repeat dose toxicity

In the non-clinical toxicity studies, which were performed in normocythemic animals with a fixed dosing regimen of methoxy polyethylene glycol-epoetin beta of up to 30 μg/kilogram (kg)/dose once weekly caused various adverse changes including mortality and serious pathogenesis secondary to an exaggerated pharmacological effect resulting in polycythemia. The serious pathological findings characterized as vascular congestion, hemorrhage, thrombosis, necrosis, and/or inflammation in various organs and tissues were associated with uncontrolled polycythemia in the affected animals.

Relevance to human usage:

No.

Discussion:

These findings seen in normal animals with uncontrolled stimulation of erythropoiesis are unlikely to be encountered in clinical practice, where the dose will be adjusted on the basis of measured Hb, which is regularly monitored, to maintain the Hb level in the target range as outlined in the European Union (EU) Summary of Product Characteristics (SmPC) (Section 4.2).

1.1.2 Reproductive toxicity

When methoxy polyethylene glycol-epoetin beta was administered (up to 50 μg/kg/dose once weekly by SC injection) to male and female rats prior to and during mating, reproductive performance, fertility, and sperm assessment parameters were not affected.

Relevance to human usage:

No.

Discussion:

No reproductive toxicity was observed in the non-clinical studies.

1.1.3 Developmental toxicity

No evidence of a direct embryotoxic, fetotoxic, or teratogenic potential was identified for methoxy polyethylene glycol-epoetin beta in rats and rabbits when dosed up to 50 ug/kg/dose every three days.

Relevance to human usage:

Yes.

Discussion:

Polycythemia as a result of uncontrolled stimulation of erythropoiesis my lead to the associated adverse vascular effects as described above and have a negative impact on fetal growth.

1.2 SAFETY CONCERNS FROM NON-CLINICAL STUDIES / REDUCTION IN FETAL WEIGHT

1.2.1 Repeat dose toxicity

Repeated once weekly dosing with a fixed dosing regimen of methoxy polyethylene glycol-epoetin beta of up to 30 μg/kg/dose, resulted in an exaggerated pharmacological effect resulting in polycythemia. The serious pathological findings characterized as vascular congestion, hemorrhage, thrombosis, necrosis, and/or inflammation in various organs and tissues were associated with uncontrolled polycythemia in the affected animals as elaborated before under “exaggerated erythropoiesis”.

Relevance to human usage:

No.

Discussion:

These findings seen in normal animals with uncontrolled stimulation of erythropoiesis are unlikely to be encountered in clinical practice, where the dose will be adjusted on the basis of measured Hb, which is regularly monitored, to maintain the Hb level in the target range as outlined in the EU SmPC (Section 4.2).

1.2.2 Reproductive toxicity:

When methoxy polyethylene glycol-epoetin beta was administered (up to 50 μg/kg/dose once weekly by SC injection) to male and female rats prior to and during mating, reproductive performance, fertility, and sperm assessment parameters were not affected.

Relevance to human usage:

No.

Discussion:

No reproductive toxicity was observed in the non-clinical studies.

1.2.3 Developmental toxicity

No evidence of a direct embryotoxic, fetotoxic, or teratogenic potential was identified for methoxy polyethylene glycol-epoetin beta. The adverse effects observed were a reduction in fetal weights which occurred at doses causing maternal toxicity secondary to exaggerated pharmacodynamic effects (5 μg/kg/ dose and higher once every three days).

A significant reduction in growth rate of the F1 generation was observed during lactation and early post-weaning period; however, no effect on reflex, physical and cognitive development or reproductive performance was observed in the F1 generation of any dose groups.

Relevance to human usage:

No.

Discussion:

There are no data from the use of methoxy polyethylene glycol-epoetin beta in pregnant women.

No significant placental transfer of methoxy polyethylene glycol-epoetin beta was observed in the rat and animal studies. Results do not indicate direct harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development.

There was, however, a class-related reduction in fetal weight and a decrease in postnatal body-weight gain of off springs at the doses causing exaggerated pharmacodynamic effects in mothers. Physical, cognitive, or sexual developments in the offspring of mothers receiving methoxy polyethylene glycol-epoetin beta during gestation and lactation were not affected.

1.3 SAFETY CONCERNS FROM NON-CLINICAL STUDIES / GROWTH FACTOR POTENTIAL AND POTENTIAL TUMOR INDUCTION

1.3.1 Repeat dose toxicity

Methoxy polyethylene glycol-epoetin beta did not induce a proliferative response in non-hematological tumor cell lines in vitro. In human tissues, the in vitro binding of methoxy polyethylene glycol-epoetin beta was only observed in target cells (bone marrow progenitor cells). Preclinical studies did not indicate growth stimulation potential of methoxy polyethylene glycol-epoetin beta in various non-target human cells. The

carcinogenic potential of methoxy polyethylene glycol-epoetin beta has not been evaluated in animal studies beyond 6 months. In a six-month rat toxicity study no tumorigenic or unexpected mitogenic responses were observed in non-hematological tissues.

Relevance to human usage:

Yes.

Discussion:

As a class effect described for all ESAs, methoxy polyethylene glycol-epoetin beta can be viewed as a growth factor, and as with other growth factors, there is a hypothetical concern that methoxy polyethylene glycol-epoetin beta could act as a growth factor for human tumor types. However, to date no respective evidence has been observed in preclinical or clinical studies with methoxy polyethylene glycol-epoetin beta.

1.3.2 Reproductive toxicity

When methoxy polyethylene glycol-epoetin beta was administered (up to 50 μg/kg/dose once weekly by SC injection) to male and female rats prior to and during mating, reproductive performance, fertility, and sperm assessment parameters were not affected.

Relevance to human usage:

No.

Discussion:

No reproductive toxicity was observed in the non-clinical studies.

1.3.3 Developmental toxicity

No evidence of a direct embryotoxic, fetotoxic, or teratogenic potential was identified for methoxy polyethylene glycol-epoetin beta.

Relevance to human usage:

Yes.

Discussion:

Polycythemia as a result of uncontrolled stimulation of erythropoiesis may lead to the associated adverse vascular effects as described above and may have a negative impact on fetal growth.

1.4 SAFETY CONCERNS FROM NON-CLINICAL STUDIES / ANTI-ERYTHROPOIETIN ANTIBODY DEVELOPMENT

1.4.1 Repeat dose toxicity

As expected when heterologous human protein is introduced to animal species, some individual rats and dogs developed anti-erythropoietin antibodies following repeated administrations of methoxy polyethylene glycol-epoetin beta, and at the same time developed resistance to once weekly administration of methoxy polyethylene glycol-epoetin beta, resulting in anemia. Resistance to methoxy polyethylene glycol-epoetin beta following repeated treatment observed in animal studies is considered a reflection of the presence of neutralizing antibodies to methoxy polyethylene glycol-epoetin beta and endogenous EPO in these animals.

Relevance to human usage:

Yes.

Discussion:

The development of antibodies in dogs and rats exposed to a human-derived biotechnology product is not predictive of immunogenicity of methoxy polyethylene glycol-epoetin beta in humans.

However, anti-erythropoietin antibody (AEAB)-mediated pure red cell aplasia (PRCA) is considered a potential risk for humans receiving ESAs. Sudden loss of response to methoxy polyethylene glycol-epoetin beta should be evaluated for its etiology.

1.4.2 Reproductive toxicity

When methoxy polyethylene glycol-epoetin beta was administered (up to 50 μg/kg/dose once weekly by SC injection) to male and female rats prior to and during mating, reproductive performance, fertility, and sperm assessment parameters were not affected.

Relevance to human usage:

No.

Discussion:

No adverse effect on reproduction was identified.

1.4.3 Developmental toxicity

No evidence of a direct embryotoxic, fetotoxic, or teratogenic potential was identified for methoxy polyethylene glycol-epoetin beta.

Relevance to human usage:

No.

Discussion:

No adverse effect on embryo development was identified.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

A total of 15 clinical studies were conducted to evaluate the safety of methoxy polyethylene glycol-epoetin beta in clinical use in the development program (cut-off date: 8 October 2010). Four Phase II studies, and six pivotal Phase III studies that supported the original marketing authorization application, and the four Phase III/IIIb studies and one Phase IV study completed since the original approval were included in the integrated analysis.

Duration of exposure to methoxy polyethylene glycol-epoetin beta (Table 2), exposure by age group and gender (Table 3), exposure by ethnic or racial origin (Table 4) and exposure in special populations (Table 5) from these 15 clinical studies are shown in Table 2 – Table 5 , respectively.

Table 2 Duration of Exposure

Duration of Exposure	Persons (%)	Person Time (years)
At least 1 month	3665 (98.8)	303.03
At least 3 months	3490 (94.1)	905.00
At least 6 months	3181 (85.8)	1740.99
At least 12 months	2485 (67.0)	3121.69
At least 2 years	1580 (42.6)	4882.48
At least 3 years	1211 (32.7)	6282.75
At least 4 years	853 (23.0)	7311.65
At least 5 years	528 (14.2)	8012.40
At least 6 years	322 (8.7)	8436.34
At least 7 years	151 (4.1%)	8667.93
At least 8 years	19 (0.5)	8752.55
TOTAL	**3708 (100)**	**8755.80**

Duration of Exposure	Persons (%)	Person Time (years)
Includes data from studies: BA16260, BA16528, BA16285, BA16286 (Phase II studies) and BA16736, BA16738, NH20052, BA16739, BA16740, BA17283, BA17284, BH17847, BH20051, BH18387 (Phase III/IIIb studies) and BH21260 (Phase IV post-authorization safety study).		

Table 3 Age Group and Gender

Age Group	Persons		Person Time (years)	
	M	F	M	F
<65 years	1062	826	2491.9	2123.7
65-74 years	533	420	1250.1	1024.4
≥75 years	506	361	1082.8	782.9
TOTAL	**2101**	**1607**	**4824.8**	**3931.0**
Includes data from studies: BA16260, BA16528, BA16285, BA16286 (Phase II studies) and BA16736, BA16738, NH20052, BA16739, BA16740, BA17283, BA17284, BH17847, BH20051, BH18387(Phase III/IIIb studies) and BH21260 (Phase IV post-authorization safety study).				

Table 4 Ethnic or Racial Origin

Ethnic/Racial Origin	Persons	Person Time (years)
Black	405	809.0
Caucasian	2948	6965.0
Oriental	271	714.1
Other	84	267.7
TOTAL	**3708**	**8755.8**
Includes data from studies: BA16260, BA16528, BA16285, BA16286 (Phase II studies) and BA16736, BA16738, NH20052, BA16739, BA16740, BA17283, BA17284, BH17847, BH20051, BH18387 (Phase III/IIIb studies) and BH21260 (Phase IV post-authorization safety study).		

Table 5 Special Population Exposure

Indication	Treatment of symptomatic anemia associated with CKD	
	Number of Patients	**PEY**
Pregnant women		
No	1607*	3931.0
CV disease at baseline**		
No	77	135.8
Yes	3195	7819.4
Study design		
Correction	845	1960.0
Maintenance	2863	6795.8
Route of study drug administration		
IV	2004	4744.1
SC	1704	4011.7
Mode of current dialysis		
HD	2848	6829.6
PD	154	356.7
Not yet on dialysis	706	1569.4
Schedule of Study Drug Administration		
1x/week	136	188.4
1x/2 weeks	1385	3230.3
1x/3 weeks	88	128.3
1x/4 weeks or 1x/month	2099	5208.8
Diabetes Status		
Diabetic	1397	3052.0
Non-diabetic	2311	5703.8
All Patients	**3708**	**8755.8**

*3 women (2 Mircera, 1 reference) became pregnant during PASS BH21260 and gave birth to a normal child.

**Cardiovascular disease at baseline only in patients defined as having one of the following risk factors: diabetes, arterial hypertension or hyperlipidemia.

CKD=chronic kidney disease, PD=pharmacodynamics, PEY=patient exposure years, CVD= cardiovascular disease, IV=intravenous, SC=subcutaneous, HD=hemodialysis.

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

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

Exclusion criteria were similar across the clinical trials of the methoxy polyethylene glycol-epoetin beta development program. Patients aged less than 18 years were excluded from all trials. Patients with causes of anemia other than CKD or with conditions known to compromise response to ESA treatment were excluded.

Table 6 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
Known hypersensitivity to recombinant human erythropoietin (rhuEPO), polyethylene glycol (PEG) or any other constituent of methoxy polyethylene glycol-epoetin beta	Hypersensitivity is a rare occurrence however, patients with known hypersensitivity should not be treated with methoxy polyethylene glycol-epoetin beta.	No	Hypersensitivity is a rare occurrence. Patients with known hypersensitivity should not be treated with methoxy polyethylene glycol-epoetin beta. If hypersensitivity occurs, treatment with methoxy polyethylene glycol-epoetin beta must be discontinued. 'Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.' is included in the EU SmPC, in Section 4.3, Contraindications.
Poorly controlled hypertension	Blood pressure (BP) should be adequately controlled in all patients before, at initiation of, and during treatment with methoxy polyethylene glycol-epoetin beta. If high BP is difficult to control by medical treatment or dietary measures, the dose must be reduced or administration discontinued.	No	Uncontrolled hypertension is included in the EU SmPC, in Section 4.3, Contraindications.
Overt GI bleeding or any other bleeding episode necessitating transfusion	Potential impact on the assessment of the efficacy of methoxy polyethylene glycol-epoetin beta.	No	The safety and efficacy of methoxy polyethylene glycol-epoetin beta therapy has not been established in patients with bleeding or a recent history of bleeding requiring transfusions. Therefore, caution should be used in these patients, see Section 4.4 in the EU SmPC.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Hemoglobinopathies	Potential impact on the assessment of the efficacy of methoxy polyethylene glycol-epoetin beta.	No	This exclusion criterion was not related to the safety of the patient population. The safety and efficacy of methoxy polyethylene glycol-epoetin beta therapy has not been established in patients with hemoglobinopathies. Caution should be used in these patients, see Section 4.4 in the EU SmPC.
Hemolysis	Potential impact on the assessment of the efficacy of methoxy polyethylene glycol-epoetin beta.	No	This exclusion criterion was not related to the safety of the patient population. It is described in Section 4.4 in the EU SmPC that hemolysis may compromise the erythropoietic response, and should be corrected in the presence of failure to respond to methoxy polyethylene glycol-epoetin beta.
Active malignant disease (except non-melanoma skin cancer)	Potential impact on withdrawal rate and duration of observation, thereby affecting assessment of efficacy and safety. As with all growth factors, there is a concern that ESAs could stimulate the growth of any type of malignancy.	No	This exclusion criterion was not related to the safety of the patient population. Effect on tumor growth has been adequately described in Sections 4.4 and 5.1 in the EU SmPC.
Chronic, uncontrolled, or symptomatic inflammatory disease (e.g., rheumatoid arthritis, systemic lupus erythematosus) - Acute infection - Elevated C-reactive protein (CRP) - Temporary (untunelled) dialysis access catheter	Inflammation and infection have a potential impact on the assessment of the efficacy of methoxy polyethylene glycol-epoetin beta.	No	This exclusion criterion was not related to the safety of the patient population. It is described in Section 4.4 in the EU SmPC that inter-current infections and inflammatory episodes may compromise the erythropoietic response, and should be corrected in the presence of failure to respond to methoxy polyethylene glycol-epoetin beta.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Vitamin B12 deficiency - Folic acid deficiency	Potential impact on the assessment of the efficacy of methoxy polyethylene glycol-epoetin beta. Deficiencies of folic acid or vitamin B12 reduce the effectiveness of ESAs and should therefore be corrected	No	This exclusion criterion was not related to the safety of the patient population. It is described in Section 4.4 in the EU SmPC that deficiencies of folic acid or vitamin B12 reduce the effectiveness of ESAs, and should be corrected in the presence of failure to respond to methoxy polyethylene glycol-epoetin beta.
Uncontrolled or symptomatic secondary hyperparathyroidism	Potential impact on the assessment of the efficacy of methoxy polyethylene glycol-epoetin beta.	No	This exclusion criterion was not related to the safety of the patient population. It is described in Section 4.4 in the EU SmPC that failure to respond to methoxy polyethylene glycol-epoetin beta should prompt for a search for causative factors.
Epileptic seizures	Previous experience with other ESAs has led to a general precaution on their use in patients with epileptic seizures.	No	The safety and efficacy of methoxy polyethylene glycol-epoetin beta therapy has not been established in patients with epileptic seizures Therefore, caution should be used in these patients. This has been adequately described in Section 4.4 of the EU SmPC.
Platelet count > 500 × 109/L	Previous experience with other ESAs has led to a general precaution on their use in patients with thrombocytosis.	No	The safety and efficacy of methoxy polyethylene glycol-epoetin beta therapy has not been established in patients with platelet levels greater than 500 x 109/L. Therefore, caution should be used in these patients - see Section 4.4 in the EU SmPC.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Pure red cell aplasia	PRCA caused by AEAB has been reported in association with all marketed ESAs.	No	In case PRCA is diagnosed, therapy with methoxy polyethylene glycol-epoetin beta must be discontinued, and patients should not be switched to another recombinant erythropoietic protein. PRCA is included in the EU SmPC, in Sections 4.4 and 4.8.
High likelihood of early withdrawal or interruption of the study (e.g. MI, severe or unstable coronary artery disease, stroke, severe liver disease within the 12 weeks before screening).	Potential impact on withdrawal rate and duration of observation, thereby affecting assessment of efficacy and safety.	No	This exclusion criterion was not related to the safety of the patient population, and applied to clinical trials only.
Pregnancy or breastfeeding - Women of childbearing potential without effective contraception	The safety and efficacy of ESAs have not been established in pregnant or breastfeeding women.	No	Section 4.4 of the EU SmPC adequately describes the information regarding pregnancy or breast feeding. Caution should be exercised when prescribing methoxy polyethylene glycol-epoetin beta to pregnant women.

AEAB=anti-erythropoietin antibody; BP=blood pressure; CRP=C-reactive protein; ESA= erythropoiesis stimulating agent; PEG=polyethylene glycol, PRCA=pure red cell aplasia; RhuEPO=recombinant human erythropoietin.

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

The clinical development program is unlikely to detect certain types of adverse 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 PROGRAMS

Table 7 Exposure of special populations included or not in clinical trial development program

Type of special population	Exposure
Pregnant women and women of childbearing potential.	Not included in the clinical development program.
Breastfeeding women.	Not included in the clinical development program.
Patients with relevant comorbidities:	
Patients with hepatic impairment: Patients with severe liver disease within the 12 weeks before screening were excluded from the clinical program. Following the results of study BP20483 investigating the effect of severe hepatic impairment on the pharmacokinetics of methoxy polyethylene glycol-epoetin beta, the EU SmPC was amended.	12 patients (severe hepatic impairment).
Patients with cardiovascular impairment*	3195 patients.
Patients with GI bleeding or any other bleeding episode necessitating transfusion before screening.	Patients were not excluded from PASS BH21260. 76 patients with GI hemorrhage.
Patients with chronic inflammatory disease (elevated CRP, chronic, uncontrolled or symptomatic inflammatory disease {e.g. rheumatoid arthritis, systemic lupus erythematosus}).	Patients with elevated CRP were not excluded from PASS BH21260. 96 patients with CRP>30mg/L.

Type of special population	Exposure
Patients with active malignant disease (except non-melanoma skin cancer).	Patients were not excluded from PASS BH21260. 142 patients with current disease at baseline in SCT neoplasms benign, malignant and unspecified (including cysts and polyps).
Immunocompromised patients.	52 patients with HIV.
Population with relevant different racial and/or ethnic origin.	There were no exclusions based on race or ethnicity in the methoxy polyethylene glycol-epoetin beta clinical program; exposure data by race is found in Table 4.
Sub-populations carrying known and relevant polymorphisms.	Not included in the clinical development program.
Other:	
Children.	Patients aged less than 18 years were excluded from the adult clinical development program. However, a paediatric program was conducted and completed in December 2021. It included two clinical studies: a Phase II dose-finding study (NH19707) in CKD patients on HD aged 5 years to < 18 years in the maintenance treatment of anemia (completed in April 2016) and a second Phase II study (NH19708, completed in December 2021) to confirm the optimal starting dose of methoxy polyethylene glycol-epoetin beta given subcutaneously for the maintenance treatment of anemia in pediatric patients with CKD aged 3 months to < 18 years on dialysis and not yet on dialysis. Approval from EMA for Extension of indication to include treatment of paediatric patients from 3 months to less than 18 years of age who are converting from another erythropoiesis stimulating agent (ESA) after their haemoglobin level was stabilised with the previous ESA was received on Positive opinion on 22 June 2023 and commission decision on 26 July 2023.

*Cardiovascular disease at baseline only in patients defined as having one of the following risk factors: diabetes, arterial hypertension or hyperlipidemia.

CKD=chronic kidney disease; CRP= C-reactive protein; GI=gastrointestinal; HD = hemodialysis; PASS = Post-authorization safety study; PK=pharmacokinetics.

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORISATION EXPOSURE

SV.1.1 Method used to calculate exposure

To estimate the number of patients treated with Roche's medications, two different calculation approaches are used, each generating two types of patient estimates:

- Interval patient count
- Cumulative patient count (since international birth date [IBD])

Both approaches rely on converting sales volume into the estimated number of patients based on assumptions about the dosage consumed per patient over a given time period. However, the key difference lies in how the sales data is interpreted:

- **Approach 1:** Aggregates sales volume for a specific time period.
- **Approach 2:** Tracks sales fluctuations to identify changes in patient dynamics.

Sales Volume Aggregation Approach (Approach 1)

Primarily used for products with more simple treatment/dosing regimens, this approach use the estimated patient numbers by aggregating sales volume over a defined period and dividing it by the assumed dose per patient within that period. This method can also incorporate compliance and persistence factors to refine estimates.

- The **interval patient count** represents the number of active patients during a specific period.
- The **cumulative patient count**: Adds up interval counts over time, reflecting ongoing treatment.

This approach has traditionally been considered the gold standard, though it has limitations for long-term or lifetime treatments, where it is not sensitive enough to distinguish between new and continuing patients, which can lead to overlapping count of interval data when compiling cumulative exposure. This can lead to the overestimated exposure, which needs to be avoided.

Monthly Sales Volume Fluctuation Approach (Approach 2)

Designed for long-term treatments and more complex dosing regimens (that does not allow to calculate an average dose per patient), this approach tracks monthly **sales fluctuations** to infer patient dynamics. Increases suggest the entry of **new patients** into

the treatment pool; decreases of sales might indicate patients drop-out from the treatment

- The **interval patient count** includes both new and continuing patients, with adjustments for drop-outs. This ensures the count of patients reflects only those actively participating in treatment during each interval.
- The **cumulative patient count** is derived by summing all new patients over time, avoiding the risk of double counting that could occur in the first approach (e.g., maintenance patients).

Over the life cycle of a product, the approach for patient exposure estimation may change.

Approach 2 is sensitive to fluctuations in sales data, which especially in the period following product launch can show high variability. These fluctuations are often influenced by stockpiling, the scale of which is uncertain and cannot be reliably estimated at an early stage.

In addition, Approach 2 may include specific assumptions, such as the persistence curve and values derived from claims data. These assumptions require a sufficient amount of post-launch data, which typically becomes available only after a certain time has passed.

For this reason, Approach 1 may be more suitable during the initial phase. It uses aggregated sales data, which helps to reduce the impact of early stockpiling, and allows for the use of average-based assumptions rather than detailed, time-specific inputs.

In summary, although Approach 2 is more appropriate for the certain product's therapeutic profile, it may not be practical to apply it immediately after launch due to early data variability and limited availability of required inputs. A staged approach—starting with Approach 1 and transitioning to Approach 2 as data matures—may be preferred.

This estimate of the global exposure of patients treated with commercial supply of Mircera was derived from the number of galenical units sold for each formulation with the exception of exposure in the U.S. (see below). Volume data for Mircera is sourced from Roche supply chain and financial systems (Controlling Profitability Analysis). The sales records are provided on a monthly basis; therefore, cumulative exposure is available from IBD (20 July 2007) to the nearest point to the DLP (19 July 2025).

The data from the Marketing Authorization Holder (MAH)s/out-licensing partner in Japan (Chugai) are included.

In order to convert the galenical units (i.e., number of syringes) to patients, the following assumptions have been applied uniformly across all geographies with the exception of the U.S.:

- Every syringe with a dose 75 μg or above = 1 patient month
- For 25 μg (Chugai), 30 μg (Roche) and 50 μg syringes:
  - 50% usage in maintenance therapy: 1 syringe = 1 patient month
  - 25% usage in correction: 2 syringes = 1 patient month
  - 25% usage in correction monthly formulation: 1 syringe = 1 patient month

Patient exposure for U.S. is provided by the license partner Vifor. The patient exposure is based on volume sold and an average use of 150 ug Mircera per Month/per patient in the US dialysis setting.

SV.1.2 Exposure

From the IBD to 19 July 2025, the estimated worldwide cumulative marketing exposure to methoxy polyethylene glycol-epoetin beta was 5.6 million patient years. Detailed presentation of Cumulative Exposure from Marketing Experience is presented in Annex 7.

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

POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

In the 1970s, autologous and homologous transfusions referred to as blood doping were misused to enhance performance. In addition, the potential of misuse of ESAs to enhance athletic performance by increasing Hb levels is known especially in endurance sports because of the expected increase in aerobic performance since the 1980s. Hematocrit and Hb can reach dangerous levels. In addition lack of medical supervision and fluid loss during endurance can increase the risk of Serious Adverse Event (SAEs) associated with an increase in viscosity due to misuse (Kennedy 2000; Robinson et al. 2003; Scott 1990).

The issue is addressed in Section 4.4 of the EU SmPC.

Nineteen cases of methoxy polyethylene glycol-epoetin beta misuse for doping have been reported in the global safety database. These cases were spontaneous reports and mainly concerned participants of the Beijing Olympics in 2008 and the “Tour de France” bicycle race in 2008. No adverse events associated with this misuse were reported.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

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

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

Not applicable

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:

No important identified risks are associated with methoxy polyethylene glycol-epoetin beta.

Information on Potential Risks:

Tumor Growth Promotion

Potential mechanisms:

Erythropoietin receptors may be expressed on the surface of a variety of tumor cells. As with all growth factors, there is a concern that ESAs could stimulate the growth of any type of malignancy. The results from preclinical studies suggest that it is unlikely that methoxy polyethylene glycol-epoetin beta has the potential to stimulate growth of normal or malignant human cells other than erythroid progenitor cells in the bone marrow. The exclusive binding profile to cell surface Epo-R on the erythroid progenitor cells in the bone marrow (Roche Report 1015621, available on request) also suggests that nonspecific binding of methoxy polyethylene glycol-epoetin beta to other receptor or other cell types to stimulate proliferation is unlikely.

Evidence source and strength of evidence:

- Preclinical studies
- Clinical studies
- Meta-analysis of 53 clinical studies

Tumor growth promotion is considered a potential risk of the ESA class. However, there is no direct evidence of tumor growth promotion for methoxy polyethylene glycol-epoetin beta. In the meta-analysis which provides strongest evidence for ESAs to date, there is no study with methoxy polyethylene glycol-epoetin beta [Bohlius et al. 2009].

Characterization of the risk:

Survival and tumor progression have been examined in five large, controlled studies involving a total of 2,833 patients, of which four were double-blind placebo-controlled studies and one was an open-label study. Two of the studies recruited patients who were being treated with chemotherapy. The target hemoglobin concentration in two studies was >13 g/dl; in the remaining three studies it was 12-14 g/dl. In the open-label study there was no difference in overall survival between patients treated with recombinant human erythropoietin and controls. In the four placebo-controlled studies the hazard ratios for overall survival ranged between 1.25 and 2.47 in favor of controls. These studies have shown a consistent unexplained statistically significant excess mortality in patients who have anemia associated with various common cancers who received recombinant human erythropoietin compared to controls. Overall survival outcome in the trials could not be satisfactorily explained by differences in the incidence of thrombosis and related complications between those given recombinant human erythropoietin and those in the control group [Recombinant human erythropoietins: new advice for prescribing].

A patient-level data analysis has also been performed on more than 13,900 cancer patients (chemo-, radio-, chemoradio-, or no therapy) participating in 53 controlled clinical trials involving several epoetins. Meta-analysis of overall survival data produced a hazard ratio point estimate of 1.06 in favor of controls (95% CI: 1.00, 1.12; 53 trials and 13,933 patients) and for the cancer patients receiving chemotherapy, the overall survival hazard ratio was 1.04 (95% CI: 0.97, 1.11; 38 trials and 10,441 patients). Meta-analyses also indicate consistently a significantly increased relative risk of thromboembolic events in cancer patients receiving recombinant human erythropoietin. No patients treated with methoxy polyethylene glycol-epoetin beta were included in this data analysis [Bohlius et al. 2009].

Methoxy polyethylene glycol-epoetin beta is not approved for treatment of patients with chemotherapy induced anemia. It is available as a solution for injection in pre-filled syringes with dose strengths up to 360 micrograms, designed for the approved indication of CKD anemia only. Other ESAs approved in anemic cancer patients receiving chemotherapy include epoetin alfa, epoetin beta and darbepoetin, however the recommended dose for these cancer patients is much higher than the dose for anemic CKD patients [SmPCs for Eprex, Neorecormon, Aranesp]. Theoretically, for methoxy polyethylene glycol-epoetin beta, reaching a clinically comparable dose with once monthly administration in patients with chemotherapy induced anemia is challenging. The off-label use of methoxy polyethylene glycol-epoetin beta in this population is

therefore minimal (8 case reports from MAH's safety database in the context of 1.9 million patient-years of exposure since International Birth Date) [Mircera PBRER 1079144].

Risk factors and risk groups:

Risk factors or risk groups have not been established for tumor growth promotion under methoxy polyethylene glycol-epoetin beta treatment.

Preventability

Methoxy polyethylene glycol-epoetin beta is not approved and should not be used to treat patients with chemotherapy induced anemia. Preventability of tumor growth promotion under methoxy polyethylene glycol-epoetin beta treatment is unknown.

Impact on the benefit risk balance of the product:

The safety and efficacy of methoxy polyethylene glycol-epoetin beta therapy in cancer anemia patients has not been established. Methoxy polyethylene glycol-epoetin beta is not approved in cancer anemia patients. No clinical development is being pursued or planned in this indication. However, there are currently ongoing clinical trials in this indication for other ESAs.

Public health impact:

As outlined above, the impact on public health is expected to be minimal due to the very limited off-label use of methoxy polyethylene glycol-epoetin beta in cancer anemia patients and lack of direct evidence of tumor growth promotion in association with methoxy polyethylene glycol-epoetin beta.

SVII.3.2. Presentation of the Missing Information

Information on Missing Information:

No missing information is associated with methoxy polyethylene glycol-epoetin beta.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 8 Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Tumour growth progression
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: Not applicable

Annex 4 is not applicable as the monitoring program for AEAB-mediated PRCA for Mircera is now being removed subsequent to discontinuation of AEAB free testing offer

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Routine PV activities are considered by the MAH/Applicant to be sufficient to obtain and analyze relevant post-marketing safety data for all safety concerns with the aim to fully assess the safety of the product.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

There are no imposed mandatory additional PV activities which are conditions of the marketing authorization or imposed mandatory additional PV activities which are specific obligations in the context of a conditional marketing authorization/marketing authorization under exceptional circumstances or that which require additional PV activities. This section is therefore not applicable.

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are currently no post-authorization efficacy studies ongoing for methoxy polyethylene glycol-epoetin beta.

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

V RISK MINIMIZATION PLAN

V.1 ROUTINE RISK MINIMIZATION MEASURES

Table 9 Description of Routine Risk Minimization Measures by Safety Concern

Safety concern(s)	Routine risk minimization activities
Tumor growth progression	**Routine risk communication:** SmPC section 4.4, Special warnings and precautions for use SmPC section 5.1, Pharmacodynamic properties **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Legal Status: Mircera is a prescription only medicine.
SmPC=summary of product characteristics.	

V.2. ADDITIONAL RISK MINIMIZATION MEASURES

No additional risk minimization measures available.

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

Not applicable.

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PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR METHOXY POLYETHYLENE GLYCOL-EPOETIN BETA

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

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

This summary of the RMP for Mircera 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 Mircera RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Mircera is authorized for the treatment of symptomatic anemia associated with chronic kidney disease (see SmPC for the full indication). It contains methoxy polyethylene

glycol-epoetin beta as the active substance and it is given by subcutaneous or intravenous route.

Further information about the evaluation of Mircera benefits can be found in Mircera 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 MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Mircera, together with measures to minimize such risks and the proposed studies for learning more about Mircera 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 PL 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 addition to these measures, information about adverse events is collected continuously and regularly analyzed, including Periodic Safety Update report (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 Mircera are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered or taken. 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 Mircera. 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	None
Important potential risks	Tumor growth progression
Missing information	None

II.B SUMMARY OF IMPORTANT RISKS

Important potential risk: Tumor growth progression	
Evidence for linking the risk to the medicine	• Preclinical studies • Clinical studies • Meta-analysis of 53 clinical studies Tumor growth promotion is considered a potential risk of the ESA class. However, there is no direct evidence of tumor growth promotion for methoxy polyethylene glycol-epoetin beta. In the meta-analysis which provides strongest evidence for ESAs to date, there is no study with methoxy polyethylene glycol-epoetin beta.
Risk factors and risk groups	Risk factors or risk groups have not been established for tumor growth promotion under methoxy polyethylene glycol-epoetin beta treatment.
Risk-minimization measures	**Routine risk-minimization measures:** **Routine risk communication:** SmPC section 4.4, Special warnings and precautions for use SmPC section 5.1, Pharmacodynamic properties **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Legal Status: Mircera is a prescription only medicine.

ESA=erythropoietin stimulating agent; SmPC=Summary of Product Characteristics.

II.C POST-AUTHORIZATION DEVELOPMENT PLAN

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

None

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

None

ANNEX 4

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

NOT APPLICABLE

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES

NOT APPLICABLE

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