SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MIRCERA 30 micrograms/0.3 ml solution for injection in pre-filled syringe
MIRCERA 50 micrograms/0.3 ml solution for injection in pre-filled syringe
MIRCERA 75 micrograms/0.3 ml solution for injection in pre-filled syringe
MIRCERA 100 micrograms/0.3 ml solution for injection in pre-filled syringe
MIRCERA 120 micrograms/0.3 ml solution for injection in pre-filled syringe
MIRCERA 150 micrograms/0.3 ml solution for injection in pre-filled syringe
MIRCERA 200 micrograms/0.3 ml solution for injection in pre-filled syringe
MIRCERA 250 micrograms/0.3 ml solution for injection in pre-filled syringe
MIRCERA 360 micrograms/0.6 ml solution for injection in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

MIRCERA 30 micrograms/0.3 ml solution for injection in pre-filled syringe
One pre-filled syringe contains 30 micrograms of methoxy polyethylene glycol-epoetin beta* at a concentration of 100 micrograms/ml
MIRCERA 50 micrograms/0.3 ml solution for injection in pre-filled syringe
One pre-filled syringe contains 50 micrograms of methoxy polyethylene glycol-epoetin beta* at a concentration of 167 micrograms/ml.
MIRCERA 75 micrograms/0.3 ml solution for injection in pre-filled syringe
One pre-filled syringe contains 75 micrograms of methoxy polyethylene glycol-epoetin beta* at a concentration of 250 micrograms/ml
MIRCERA 100 micrograms/0.3 ml solution for injection in pre-filled syringe
One pre-filled syringe contains 100 micrograms of methoxy polyethylene glycol-epoetin beta* at a concentration of 333 micrograms/ml.
MIRCERA 120 micrograms/0.3 ml solution for injection in pre-filled syringe
One pre-filled syringe contains 120 micrograms of methoxy polyethylene glycol-epoetin beta* at a concentration of 400 micrograms/ml.
MIRCERA 150 micrograms/0.3 ml solution for injection in pre-filled syringe
One pre-filled syringe contains 150 micrograms of methoxy polyethylene glycol-epoetin beta* at a concentration of 500 micrograms/ml.
MIRCERA 200 micrograms/0.3 ml solution for injection in pre-filled syringe
One pre-filled syringe contains 200 micrograms of methoxy polyethylene glycol-epoetin beta* at a concentration of 667 micrograms/ml
MIRCERA 250 micrograms/0.3 ml solution for injection in pre-filled syringe
One pre-filled syringe contains 250 micrograms of methoxy polyethylene glycol-epoetin beta* at a concentration of 833 micrograms/ml.
MIRCERA 360 micrograms/0.6 ml solution for injection in pre-filled syringe
One pre-filled syringe contains 360 micrograms of methoxy polyethylene glycol-epoetin beta* at a concentration of 600 micrograms/ml.

The strength indicates the quantity of the protein moiety of the methoxy polyethylene glycol-epoetin beta molecule without consideration of the glycosylation.

*Protein produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells and covalently conjugated to a linear methoxy-polyethylene glycol (PEG).

The potency of methoxy polyethene glycol-epoetin beta should not be compared to the potency of another pegylated or non-pegylated protein of the same therapeutic class. For more information, see section 5.1.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe (injection).
The solution is clear and colourless to slightly yellowish.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of symptomatic anaemia associated with chronic kidney disease (CKD) in adult patients (see section 5.1).

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 (see section 5.1).

4.2 Posology and method of administration

Treatment has to be initiated under the supervision of a physician experienced in the management of patients with renal impairment.

Posology

Treatment of symptomatic anaemia in chronic kidney disease patients
Anaemia 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. Treatment should be administered either subcutaneously or intravenously in order to increase haemoglobin to not greater than 12 g/dl (7.45 mmol/l). Subcutaneous use is preferable in patients who are not receiving haemodialysis to avoid puncture of peripheral veins.

Due to intra-patient variability, occasional individual haemoglobin values for a patient above and below the desired haemoglobin level may be observed. Haemoglobin variability should be addressed through dose management, with consideration for the haemoglobin target range of 10 g/dl (6.21 mmol/l) to 12 g/dl (7.45 mmol/l). A sustained haemoglobin level of greater than 12 g/dl (7.45 mmol/l) should be avoided; guidance for appropriate dose adjustment for when haemoglobin values exceeding 12 g/dl (7.45 mmol/l) are observed are described below.

A rise in haemoglobin of greater than 2 g/dl (1.24 mmol/l) in adult patients and 1 g/dl (0.62 mmol/l) in paediatric patients over a four-week period should be avoided. If it occurs, appropriate dose adjustment should be made as provided.

Patients should be monitored closely to ensure that the lowest approved effective dose of treatment is used to provide adequate control of the symptoms of anaemia whilst maintaining a haemoglobin concentration below or at 12 g/dl (7.45 mmol/l).

Caution should be exercised with escalation of treatment doses in patients with chronic renal failure. In patients with a poor haemoglobin response to treatment, alternative explanations for the poor response should be considered (see section 4.4 and 5.1).

It is recommended that haemoglobin is monitored every two weeks until stabilised and periodically thereafter (see section 4.4).

Adult patients not currently treated with an erythropoiesis stimulating agent (ESA):
In order to increase haemoglobin levels to greater than 10 g/dl (6.21 mmol/l), the recommended starting dose in patients not on dialysis is 1.2 microgram/kg body weight, administered once every month as a single subcutaneous injection.

Alternatively, a starting dose of 0.6 microgram/kg bodyweight may be administered once every two weeks as a single intravenous or subcutaneous injection in patients on dialysis or not on dialysis.

The dose may be increased by approximately 25% of the previous dose if the rate of rise in haemoglobin is less than 1.0 g/dl (0.621 mmol/l) over a month. Further increases of approximately 25% may be made at monthly intervals until the individual target haemoglobin level is obtained.

If the rate of rise in haemoglobin is greater than 2 g/dl (1.24 mmol/l) in one month or if the haemoglobin level is increasing and approaching 12 g/dl (7.45 mmol/l), the dose is to be reduced by approximately 25%. If the haemoglobin level continues to increase, therapy should be interrupted until the haemoglobin level begins to decrease, at which point therapy should be restarted at a dose approximately 25% below the previously administered dose. After dose interruption a haemoglobin decrease of approximately 0.35 g/dl (0.22 mmol/l) per week is expected. Dose adjustments should not be made more frequently than once a month.

Patients treated once every two weeks whose haemoglobin concentration is above 10 g/dl (6.21 mmol/l) may receive methoxy polyethylene glycol-epoetin beta administered once-monthly using the dose equal to twice the previous once-every-two-week dose.

Adult patients currently treated with an ESA:
Patients currently treated with an ESA can be switched to methoxy polyethylene glycol-epoetin beta administered once a month as a single intravenous or subcutaneous injection. The starting dose of methoxy polyethylene glycol-epoetin beta is based on the calculated previous weekly dose of darbepoetin alfa or epoetin at the time of substitution as described in Table 1. The first injection should start at the next scheduled dose of the previously administered darbepoetin alfa or epoetin.

Table 1: Methoxy polyethylene glycol-epoetin beta starting doses for adult patients currently receiving an ESA

Previous weekly darbepoetin alfa intravenous or subcutaneous dose (microgram/week)	Previous weekly epoetin intravenous or subcutaneous dose (IU/week)	Monthly methoxy polyethylene glycol-epoetin beta intravenous or subcutaneous dose (microgram/once monthly)
<40	<8,000	120
40-80	8,000-16,000	200
>80	>16,000	360

If a dose adjustment is required to maintain the target haemoglobin concentration above 10 g/dl (6.21 mmol/l), the monthly dose may be increased by approximately 25%.

If the rate of rise in haemoglobin is greater than 2 g/dl (1.24 mmol/l) over a month or if the haemoglobin level is increasing and approaching 12 g/dl (7.45 mmol/l), the dose is to be reduced by approximately 25%. If the haemoglobin level continues to increase, therapy should be interrupted until the haemoglobin level begins to decrease, at which point therapy should be restarted at a dose approximately 25% below the previously administered dose. After dose interruption a haemoglobin decrease of approximately 0.35 g/dl (0.22 mmol/l) per week is expected. Dose adjustments should not be made more frequently than once a month.

Since the treatment experience is limited in patients on peritoneal dialysis, regular haemoglobin monitoring and strict adherence to dose adjustment guidance are recommended in these patients.

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 (Table 2).

Table 2. Methoxy polyethylene glycol-epoetin beta starting doses for paediatric patients from 3 months to less than 18 years of age currently receiving an ESA

Previous weekly darbepoetin alfa dose (microgram/week)	Previous weekly epoetin dose (IU/week)	Every 4-week methoxy polyethylene glycol-epoetin beta dose (microgram)
9 - <12	2,000 - <2,700	30
12 - <15	2,700 - <3,500	50
15 - <24	3,500 - <5,500	75
24 - <30	5,500 - <6,500	100
30 - <35	6,500 - <8,000	120
35 - <47	8,000 - <10,000	150
47 - <60	10,000 - <13,000	200
60 - <90	13,000 - <20,000	250
≥90	≥20,000	360

Pre-filled syringes are not designed for administration of partial doses. Due to the available dose strengths of pre-filled syringes, paediatric patients with an ESA dose of <9 microgram/week (darbepoetin alfa) or <2,000 IU/week of epoetin, should not be switched to methoxy polyethylene glycol-epoetin beta.

If a dose adjustment is required to maintain the target haemoglobin concentration above 10 g/dl, the 4 weekly dose may be adjusted by approximately 25%.

If the rise in haemoglobin is greater than 1 g/dl (0.62 mmol/l) over 4 weeks or the haemoglobin level is increasing and approaching 12 g/dl (7.45 mmol/l), the methoxy polyethylene glycol-epoetin beta dose is to be reduced by approximately 25%.

If the haemoglobin level continues to increase following dose reduction, therapy is to be interrupted until the haemoglobin level begins to decrease, at which point therapy should be restarted at a dose approximately 25% below the previously administered dose.

Dose adjustments should not be made more often than once every 4 weeks.

Treatment interruption
Treatment is normally long-term. However, it can be interrupted at any time, if necessary.

Missed dose
If one dose of treatment is missed, the missed dose is to be administered as soon as possible and administration of treatment is to be restarted at the prescribed dosing frequency.

Paediatric population
The safety and efficacy of methoxy polyethylene glycol-epoetin beta in paediatric patients less than 3 months of age have not been established. No data are available.

Special populations

Patients with hepatic impairment
No adjustments of the starting dose nor of the dose modification rules are required in patients with hepatic impairment (see section 5.2).

Elderly population
In clinical studies 24% of patients treated with methoxy polyethylene glycol-epoetin beta were aged 65 to 74 years, while 20% were aged 75 years and over. No dose adjustment is required in patients aged 65 years or older.

Method of administration
Treatment should be administered either subcutaneously or intravenously. It can be injected subcutaneously in the abdomen, arm or thigh. All three injection sites are equally suitable. For instructions on the administration of the medicinal product, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Uncontrolled hypertension.

4.4 Special warnings and precautions for use

The safety and efficacy of methoxy polyethylene glycol-epoetin beta therapy in other indications, including anaemia in patients with cancer, has not been established. Caution should be exercised with escalation of methoxy polyethylene glycol-epoetin beta doses in patients with chronic renal failure since high cumulative epoetin doses may be associated with an increased risk of mortality, serious cardiovascular and cerebrovascular events. In patients with a poor haemoglobin response to epoetins, alternative explanations for the poor response should be considered (see section 4.2 and 5.1).

Paediatric population:

Paediatric patients, especially children <1 year of age, should be carefully evaluated before switching from another ESA treatment and the haemoglobin level should be stabilised prior to switching. Following ESA conversion, it is recommended that haemoglobin is monitored every 4 weeks.

If the current ESA dose is <9 microgram/week of darbepoetin alfa or <2,000 IU/week of epoetin, the patient should not be switched to methoxy polyethylene glycol-epoetin beta, as the lowest available pre-filled syringe dose strength is 30 micrograms. Administration of partial doses with pre-filled syringes is not recommended.

Supplementary iron therapy is recommended for all patients with serum ferritin values below 100 microgram/l or with transferrin saturation below 20%. To ensure effective erythropoiesis, iron status has to be evaluated for all patients prior to and during treatment.

Failure to respond to treatment should prompt for a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of ESAs and should therefore be corrected. Intercurrent infections, inflammatory or traumatic episodes, occult blood loss, haemolysis, severe aluminium toxicity, underlying haematologic diseases, or bone marrow fibrosis may also compromise the erythropoietic response. A reticulocyte count should be considered as part of the evaluation. If all the conditions mentioned are excluded and the patient has a sudden drop of haemoglobin associated with reticulocytopenia and anti-erythropoietin antibodies, examination of the bone marrow for the diagnosis of Pure Red Cell Aplasia (PRCA) should be considered. In case PRCA is diagnosed, treatment must be discontinued and patients should not be switched to another ESA.

Pure Red Cell Aplasia caused by anti-erythropoietin antibodies has been reported in association with all ESAs, including methoxy polyethylene glycol-epoetin beta. These antibodies have been shown to cross-react with all ESAs, and patients suspected or confirmed to have antibodies to erythropoietin should not be switched to methoxy polyethylene glycol-epoetin beta (see section 4.8).

PRCA in patients with Hepatitis C: A paradoxical decrease in haemoglobin and development of severe anaemia associated with low reticulocyte counts should prompt to discontinue treatment with epoetin and perform anti-erythropoietin antibody testing. Cases have been reported in patients with hepatitis C treated with interferon and ribavirin, when epoetins are used concomitantly. Epoetins are not approved in the management of anaemia associated with hepatitis C.

Blood pressure monitoring: As with other ESAs, blood pressure may rise during treatment with methoxy polyethylene glycol-epoetin beta. Blood pressure should be adequately controlled in all patients before, at initiation of, and during treatment with methoxy polyethylene glycol-epoetin beta. If high blood pressure is difficult to control by medical treatment or dietary measures, the dose must be reduced or administration discontinued (see section 4.2).

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported in association with epoetin treatment (see section 4.8). More severe cases have been observed with long-acting epoetins. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, methoxy polyethylene glycol-epoetin beta should be withdrawn immediately and an alternative treatment considered. If the patient has developed a severe cutaneous skin reaction such as SJS or TEN due to the use of methoxy polyethylene glycol-epoetin beta, treatment with ESA must not be restarted in this patient at any time.

Haemoglobin concentration: In patients with chronic kidney disease, maintenance haemoglobin concentration should not exceed the upper limit of the target haemoglobin concentration recommended in section 4.2. In clinical trials, an increased risk of death, serious cardiovascular events including thrombosis or cerebrovascular events including stroke was observed when ESAs were administered to target a haemoglobin of greater than 12 g/dl (7.5 mmol/l) (see section 4.8).
Controlled clinical trials have not shown significant benefits attributable to the administration of epoetins when haemoglobin concentration is increased beyond the level necessary to control symptoms of anaemia and to avoid blood transfusion.

The safety and efficacy of treatment has not been established in patients with haemoglobinopathies, seizures, bleeding or a recent history of bleeding requiring transfusions or with platelet levels greater than 500 x 10^9/l. Therefore, caution should be used in these patients.

Effect on tumour growth: Methoxy polyethylene glycol-epoetin beta, like other ESAs, is a growth factor that primarily stimulates red blood cell production. Erythropoietin receptors may be expressed on the surface of a variety of tumour cells. As with all growth factors, there is a concern that ESAs could stimulate the growth of any type of malignancy. Two controlled clinical studies in which epoetins were administered to patients with various cancers including head and neck cancers, and breast cancer, have shown an unexplained excess mortality.

Misuse of methoxy polyethylene glycol-epoetin beta by healthy people may lead to an excessive increase in haemoglobin. This may be associated with life-threatening cardiovascular complications.

Traceability: In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

This medicinal product contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially ‘sodium free’.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. There is no evidence that methoxy polyethylene glycol-epoetin beta alters the metabolism of other medicinal products.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of methoxy polyethylene glycol-epoetin beta in pregnant women. Animal studies do not indicate direct harmful effects with respect to pregnancy, embryofoetal development, parturition or postnatal development but indicate a class-related reversible reduction in foetal weight (see section 5.3). Caution should be exercised when prescribing to pregnant women.

Breast-feeding
It is unknown whether methoxy polyethylene glycol-epoetin beta is excreted in human breast milk. One animal study has shown excretion of methoxy polyethylene glycol-epoetin beta in maternal milk. A decision on whether to continue or discontinue breast-feeding or to continue or discontinue therapy with methoxy polyethylene glycol-epoetin beta should be made taking into account the benefit of breast-feeding to the child and the benefit of methoxy polyethylene glycol-epoetin beta therapy to the woman.

Fertility
Studies in animals have shown no evidence of impaired fertility (see section 5.3). The potential risk for humans is unknown.

4.7 Effects on ability to drive and use machines

Methoxy polyethylene glycol-epoetin beta has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

(a) Summary of the safety profile

The safety data base from clinical trials comprised 3,042 CKD adult patients, including 1,939 adult patients treated with methoxy polyethylene glycol-epoetin beta and 1,103 with another ESA. Approximately 6% of adult patients treated with methoxy polyethylene glycol-epoetin beta are expected to experience adverse reactions. The most frequent reported adverse reaction was hypertension (common).

(b) Tabulated list of adverse reactions
Adverse reactions in Table 3 are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 3: Adverse reactions attributed to the treatment with methoxy polyethylene glycol-epoetin beta in CKD adult patients. Adverse reactions observed only during post-marketing are marked (*).

System organ class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Uncommon	Thrombocytopenia*
	Not known	Pure red cell aplasia*
Immune system disorders	Rare	Hypersensitivity
	Not known	Anaphylactic reaction*
Nervous system disorders	Uncommon	Headache
	Rare	Hypertensive encephalopathy
Vascular disorders	Common	Hypertension
	Uncommon	Thrombosis*
	Rare	Hot flush
	Rare	Pulmonary embolism*
Skin and subcutaneous disorders	Rare	Rash, maculopapular
	Not known	Stevens-Johnson syndrome / toxic epidermal necrolysis*
Injury, poisoning and procedural complications	Uncommon	Vascular access site thrombosis

(c) Description of selected adverse reactions

Adult population

Cases of thrombocytopenia have been reported from post-marketing setting. A slight decrease in platelet counts remaining within the normal range was observed in clinical studies.
Platelet counts below 100 x 10^9/l were observed in 7% of adult patients treated with methoxy polyethylene glycol-epoetin beta and 4% of adult patients treated with other ESAs during clinical development. In a post-authorisation safety study with long treatment exposure of up to 8.4 years, baseline platelet counts below 100 x 10^9/l was present in 2.1% of adult patients in the methoxy polyethylene glycol-epoetin beta group and 2.4% of adult patients in other ESAs group. During the study, platelet counts below 100 x 10^9/l were observed yearly in 1.5% to 3.0% of adult patients treated with methoxy polyethylene glycol-epoetin beta and 1.6% to 2.5% of adult patients treated with other ESAs.

Data from a controlled clinical trial with epoetin alfa or darbepoetin alfa reported an incidence of stroke as common. A post-authorisation safety study showed similar incidence of stroke between methoxy polyethylene glycol-epoetin beta (6.3%) and reference ESAs groups (epoetin alfa, darbepoetin alfa and epoetin beta) (7%).

As with other ESAs, cases of thrombosis, including pulmonary embolism, have been reported in the post-marketing setting (see section 4.4).

Neutralising anti-erythropoietin antibody-mediated pure red cell aplasia (PRCA) has been reported, frequency unknown. 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 (see section 4.4).

Paediatric population

In the two paediatric studies, the paediatric population studied comprised a total of 104 patients, of which 12 were less than 5 years of age, 36 were 5 to 11 years of age and 56 were 12 to 17 years of age. The safety profile of methoxy polyethylene glycol-epoetin beta in the paediatric population included in these two studies was overall consistent with that known for the adult population, based on low patient exposure in these studies (see section 5.1).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The therapeutic range of methoxy polyethylene glycol-epoetin beta is wide. Individual responsiveness must be considered when treatment is initiated. Overdose can result in manifestations of an exaggerated pharmacodynamic effect, e.g. excessive erythropoiesis. In case of excessive haemoglobin levels, treatment with methoxy polyethylene glycol-epoetin beta should be temporarily discontinued (see section 4.2). If clinically indicated, phlebotomy may be performed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antianemic preparations, ATC code: B03XA03

Mechanism of action
Methoxy polyethylene glycol-epoetin beta stimulates erythropoiesis by interaction with the erythropoietin receptor on progenitor cells in the bone marrow. Methoxy polyethylene glycol-epoetin beta, the active substance of MIRCERA, is a continuous erythropoietin receptor activator that shows a different activity at the receptor level characterized by a slower association to and faster dissociation from the receptor, a reduced specific activity *in vitro* with an increased activity *in vivo*, as well as an increased half-life, in contrast to erythropoietin. The average molecular mass is approximately 60 kDa of which the protein moiety plus the carbohydrate part constitutes approximately 30 kDa.

Pharmacodynamic effects
As primary growth factor for erythroid development, the natural hormone erythropoietin is produced in the kidney and released into the bloodstream in response to hypoxia. In responding to hypoxia, the natural hormone erythropoietin interacts with erythroid progenitor cells to increase red cell production.

Clinical efficacy and safety

Adult population

Data from correction studies with patients treated once every two weeks and once every four weeks show that the haemoglobin response rates in the methoxy polyethylene glycol-epoetin beta group at the end of the correction period were high and comparable to comparators. The median time to response was 43 days in the methoxy polyethylene glycol-epoetin beta arm and 29 days in the comparator arm, with increases of haemoglobin within the first 6 weeks of 0.2 g/dl/week and 0.3 g/dl/week, respectively.

Four randomized controlled studies were performed in dialysis patients currently treated with darbepoetin alfa or epoetin at the time of enrollment. Patients were randomized to stay on their treatment at the time of enrollment or to be switched to methoxy polyethylene glycol-epoetin beta in order to maintain stable haemoglobin levels. At the evaluation period (week 29-36), the mean and median level of haemoglobin in patients treated with methoxy polyethylene glycol-epoetin beta was virtually identical to their baseline haemoglobin level.

In a randomised, double-blind, placebo-controlled study of 4,038 CRF patients not on dialysis with type 2 diabetes and haemoglobin levels ≤ 11 g/dl, patients received either treatment with darbepoetin alfa to target haemoglobin levels of 13 g/dl or placebo (see section 4.4). The study did not meet either primary objective of demonstrating a reduction in risk for all-cause mortality, cardiovascular morbidity, or end stage renal disease (ESRD). Analysis of the individual components of the composite endpoints showed the following HR (95% CI): death 1.05 (0.92, 1.21), stroke 1.92 (1.38, 2.68), congestive heart failure (CHF) 0.89 (0.74, 1.08), myocardial infarction (MI) 0.96 (0.75, 1.23), hospitalisation for myocardial ischaemia 0.84 (0.55, 1.27), ESRD 1.02 (0.87, 1.18).

Pooled post-hoc analyses of clinical studies of ESAs have been performed in chronic renal failure patients (on dialysis, not on dialysis, in diabetic and non-diabetic patients). A tendency towards increased risk estimates for all-cause mortality, cardiovascular and cerebrovascular events associated with higher cumulative ESA doses independent of the diabetes or dialysis status was observed (see section 4.2 and section 4.4).

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

Survival and tumour 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 haemoglobin 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 favour of controls. These studies have shown a consistent unexplained statistically significant excess mortality in patients who have anaemia 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.

A patient-level data analysis has also been performed on more than 13,900 cancer patients (chemo-, radia-, chemoradia-, 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 favour 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 (see section 4.4). No patients treated with methoxy polyethylene glycol-epoetin beta were included in this data analysis.
Methoxy polyethylene glycol-epoetin beta is not approved for treatment of patients with chemotherapy induced anaemia (see section 4.1 and 4.4.).

Paediatric population

Two studies have been conducted in paediatric patients. One study with intravenous administration (IV) and one study with subcutaneous administration (SC) of methoxy polyethylene glycol-epoetin beta.

The study using IV administration was a phase II, dose-finding, open-label, single-arm, multicenter, multiple dose study (NH19707) conducted in 64 paediatric patients (aged 5 to 17 years old) with CKD on hemodialysis, to evaluate two conversion factors (group 1 and group 2) in order to switch from maintenance treatment with IV epoetin alfa/beta or darbepoetin alfa to methoxy polyethylene glycol-epoetin beta, administered IV once every 4 weeks for 20 weeks. Efficacy was assessed based on the change in haemoglobin concentration (g/dl) between the baseline and evaluation period. The adjusted mean change in haemoglobin from baseline to the evaluation period in group 1 was -0.74 g/dl [95% CI: -1.32 to -0.16] and in group 2 it was -0.09 g/dl [95% CI: -0.45 to 0.26]. 58% and 75% of patients

maintained haemoglobin values within ±1 g/dl of baseline and 75% and 81% maintained haemoglobin values within 10-12 g/dl in group 1 and group 2 respectively. Subgroup analyses by age groups (5-11 years and 12-17 years) were consistent with the observations in the overall population. Patients who completed the 20 weeks of core treatment, who adequately maintained haemoglobin levels were eligible to enter an optional 52-week safety extension period with the same dosing frequency.

The study using SC administration was a second phase II, dose-finding, open-label, single-arm, multicenter study (NH19708) conducted in 40 paediatric patients (aged 3 months to 17 years old) with CKD on dialysis, or not yet on dialysis, to evaluate the conversion factor used in group 2 in the IV study, in order to switch from maintenance treatment with SC epoetin alfa/ beta or darboepoetin alfa to methoxy polyethylene glycol-epoetin beta, administered SC once every 4 weeks for 20 weeks. Similarly, in this study, the primary efficacy endpoint was the change in haemoglobin concentration (g/dl) between the baseline and evaluation period. The mean change in haemoglobin concentration during the evaluation period was 0.48 g/dl [95% CI: 0.15 to 0.82], which was within the equivalence bounds of -1 to +1g/dl. The results of the mean change in haemoglobin concentration by age group (<5 years, 5-11 years, ≥12 years) were consistent with the results of the primary endpoint during the evaluation period. Patients who completed the 20 weeks of core treatment, who adequately maintained haemoglobin levels, were eligible to enter an optional 24-week safety extension period with the same dosing frequency.

In both the studies, the mean haemoglobin values remained within 10 to 12 g/dl throughout the entire evaluation period and safety extension period for the majority of patients. The safety profile observed in paediatric patients from both studies was consistent with that found in adults (see section 4.8).

5.2 Pharmacokinetic properties

Adult population

The pharmacokinetics of methoxy polyethylene glycol-epoetin beta were studied in healthy volunteers and in anaemic patients with CKD including patients on dialysis and not on dialysis.

Following subcutaneous administration to CKD patients not on dialysis, the maximum serum concentrations of methoxy polyethylene glycol-epoetin beta were observed 95 hours (median value) after administration. The absolute bioavailability of methoxy polyethylene glycol-epoetin beta after subcutaneous administration was 54%. The observed terminal elimination half-life was 142 hours in CKD patients not on dialysis.

Following subcutaneous administration to CKD patients on dialysis, the maximum serum concentrations of methoxy polyethylene glycol-epoetin beta were observed 72 hours (median value) after administration. The absolute bioavailability of methoxy polyethylene glycol-epoetin beta after subcutaneous administration was 62% and the observed terminal elimination half-life was 139 hours in CKD patients on dialysis.

Following intravenous administration to CKD patients on dialysis, the total systemic clearance was 0.494 ml/h per kg. The elimination half-life after intravenous administration of methoxy polyethylene glycol-epoetin beta is 134 hours.

A comparison of serum concentrations of methoxy polyethylene glycol-epoetin beta measured before and after haemodialysis in 41 CKD patients showed that haemodialysis has no effect on the pharmacokinetics of this medicinal product.

An analysis in 126 CKD patients showed no pharmacokinetic difference between patients on dialysis and patients not on dialysis.

In a single dose study, after intravenous administration, the pharmacokinetics of methoxy polyethylene glycol-epoetin beta are similar in patients with severe hepatic impairment as compared to healthy subjects (see section 4.2).

Paediatric population

A population pharmacokinetic analysis was performed with data from 103 paediatric patients, aged from 6 months to 17 years, body weight ranging from 7 to 90 kg, and 524 adult patients. Paediatric patients received methoxy polyethylene glycol-epoetin beta IV (all on hemodialysis) or SC (on peritoneal dialysis, hemodialysis or not yet on dialysis). Clearance and volume of distribution were found to increase with body weight and volume of distribution with age. The observed maximum and minimum serum concentrations of methoxy polyethylene glycol-epoetin beta in paediatric patients, collected when their haemoglobin levels were stabilised, were comparable to those observed in adults for both routes of administration, IV and SC.

5.3 Preclinical safety data

Non-clinical data show no special hazard for humans based on conventional studies of cardiovascular safety pharmacology, repeat dose toxicity and reproductive toxicity.
The carcinogenic potential of methoxy polyethylene glycol-epoetin beta has not been evaluated in long-term animal studies. It did not induce a proliferative response in non-haematological tumor cell lines *in vitro*. In a six-month rat toxicity study no tumorigenic or unexpected mitogenic responses were observed in non-haematological tissues. In addition, using a panel of human tissues, the *in vitro* binding of methoxy polyethylene glycol-epoetin beta was only observed in target cells (bone marrow progenitor cells).

No significant placental transfer of methoxy polyethylene glycol-epoetin beta was observed in the rat, and studies in animals have not shown any harmful effect on pregnancy, embryofoetal development, parturition or postnatal development. There was however a class-related reversible reduction in foetal weight and a decrease in postnatal body-weight gain of offspring 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. When methoxy polyethylene glycol-epoetin beta was administered subcutaneously to male and female rats prior to and during mating, reproductive performance, fertility, and sperm assessment parameters were not affected.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium dihydrogen phosphate monohydrate
Sodium sulphate
Mannitol (E421)
Methionine
Poloxamer 188
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light.
The end-user may remove the medicinal product from refrigeration for storage at a room temperature not above 30°C for one single period of 1 month. Once removed from the refrigerator the medicinal product must be used within this period.

6.5 Nature and contents of container

Pre-filled syringe (type I glass) with laminated plunger stopper (bromobutyl rubber) and tip cap (bromobutyl rubber) and a needle 27G1/2.

Pre-filled syringes 30, 50, 75, 100, 120, 150, 200 and 250 micrograms contain 0.3 ml solution.
Pre-filled syringe 360 micrograms contains 0.6 ml solution.

Pre-filled syringes 30, 50, 75 micrograms are available in pack size of 1 or 3 pre-filled syringe(s).

Pre-filled syringes 100, 120, 150, 200, 250 and 360 micrograms are available in pack size of 1 pre-filled syringe.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The pre-filled syringe is ready for use. The sterile pre-filled syringe does not contain any preservative and is to be used for a single injection only. Only one dose should be administered per syringe. Pre-filled syringes are not designed for administration of partial doses. Only solutions which are clear, colourless to slightly yellowish and free of visible particles must be injected.
Do not shake.
Allow the pre-filled syringe to reach room temperature before injecting.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Roche Products Limited
6 Falcon Way, Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

Mircera 30 mcg : PLGB 00031/0873
Mircera 50 mcg : PLGB 00031/0876

Mircera 75 mcg : PLGB 00031/0878
Mircera 100 mcg : PLGB 00031/0868
Mircera 120 mcg : PLGB 00031/0869
Mircera 150 mcg : PLGB 00031/0870
Mircera 200 mcg : PLGB 00031/0871
Mircera 250 mcg : PLGB 00031/0872
Mircera 360 mcg : PLGB 00031/0874

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

05/05/2026