PFS-MIR-2019 03

Mircera®

Methoxy polyethylene glycol-epoetin beta

1. NAME OF THE MEDICINAL PRODUCT

MIRCERA solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Single dose pre-filled syringes: containing 50 µg, 75 µg or 100 µg methoxy polyethylene glycol-epoetin beta in 0.3 ml.

The active substance, methoxy polyethylene glycol epoetin beta, is a covalent conjugate of a protein produced by recombinant DNA technology in Chinese Hamster Ovarian cells and a linear methoxy-polyethylene glycol (PEG). This results in an approximate molecular weight of 60 kDa.

The solution is clear and colourless to slightly yellowish.

Excipients: sodium phosphate monobasic monohydrate, sodium sulphate, mannitol, methionine, poloxamer 188 and water for injection.

*Methoxy polyethylene glycol-epoetin beta is a covalent conjugate of a protein produced by recombinant DNA technology in Chinese Hamster Ovarian cells and conjugated to a linear methoxy-polyethylene glycol (PEG). This results in an approximate molecular weight of 60 kDa. The dosage strength in µg indicates the quantity of the protein moiety of the methoxy polyethylene glycol-epoetin beta molecule without consideration of the glycosylation.

3. PHARMACEUTICAL FORM

Solution for injection supplied as a sterile, ready to use liquid in:
Single dose pre-filled syringes
The solution is clear and colourless to slightly yellowish.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Treatment of anaemia associated with chronic kidney disease (CKD). The safety and efficacy of MIRCERA therapy in other indications has not been established, therefore such use is not recommended.

4.2. Posology and method of administration

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

The solution can be administered subcutaneously or intravenously.

MIRCERA can be injected subcutaneously in the abdomen, arm or thigh. All three injection sites are equally suitable.

It is recommended that haemoglobin is monitored every two weeks until stabilized and periodically thereafter.

As recommended in current guidelines, the rate of increase in Hb and the target Hb should be determined for each patient individually. In CKD patients, the aim of treatment is to reach a target Hb level of 10-12g/dL. Patients should be monitored closely to ensure that the lowest effective dose of MIRCERA is used to provide adequate control of the symptoms of anemia

Patients not currently treated with an erythropoiesis stimulating agent (ESA):
The recommended starting dose is 0.6 microgram/kg body weight, administered once every two weeks as a single intravenous or subcutaneous injection.

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 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 hemoglobin 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 per week is expected. Dose adjustments should not be made more frequently than once a month.

If the target haemoglobin concentration level of 12 g/dl (7.45 mmol/l) is reached for the individual patient, MIRCERA may be administered once monthly using the dose equal to twice the previous once every two weeks dose.

Patients currently treated with an ESA:
Patients currently treated with an ESA can be converted to MIRCERA 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: MIRCERA starting doses

Previously weekly darbepoetin alfa intravenous or subcutaneous dose (microgram/ week)	**Previously weekly epoetin intravenous or subcutaneous dose (IU/ week)**	**MIRCERA intravenous or subcutaneous dose (microgram/ once every two week)**	**Monthly MIRCERA intravenous or subcutaneous dose (microgram/ once monthly)**
< 40	< 8000	60	120
40 – 80	8000 – 16000	100	200
> 80	> 16000	180	360

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

If the rate of rise in haemoglobin is greater than 2 g/dl (1.24 mmol/l) over a month or 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 hemoglobin 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 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 Hb monitoring and strict adherence to dose adjustment guidance is recommended in these patients.

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

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

Paediatric use
MIRCERA is not recommended for use in children and adolescents below 18 years due to a lack of safety and efficacy data.

Geriatric use
In clinical studies 24% of patients treated with MIRCERA were age 65 to 74 years, while 20% were age 75 years and over. No dose adjustment is required in patients aged 65 years or older.

Hepatic impaired patients
No adjustments of the starting dose nor dose modification rules are required in patients with any degree of hepatic impairment (see section 5.4 Pharmacokinetics in Special Populations).

4.3. Contraindications

Hypersensitivity to the active substance or any of the excipients.
Patients with uncontrolled hypertension.

4.4. Special warnings and precautions for use

Supplementary iron therapy
In order to ensure effective erythropoiesis, iron status should be evaluated for all patients prior to and during treatment and supplementary iron therapy may be necessary and conducted in accordance with treatment guidelines.

Failure to respond to MIRCERA therapy 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, therapy with MIRCERA must be discontinued and patients should not be switched to another ESA.

PRCA: PRCA caused by anti-erythropoietin antibodies has been reported in association with ESAs including MIRCERA. 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 MIRCERA.

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 antierythropoietin 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.

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 erythropoiesis stimulating agents (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.

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

Effect on tumour growth: MIRCERA, 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. 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.
MIRCERA is not approved for the treatment of anaemia in patients with cancer.
The safety and efficacy of MIRCERA therapy 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.

Misuse of MIRCERA by healthy people may lead to an excessive increase in haemoglobin. This may be associated with life-threatening cardiovascular complications.

Traceability of MIRCERA: In order to improve the traceability of erythropoiesis-stimulating agents (ESAs), the trade name of the administered ESA should be clearly recorded (or stated) in the patient file.

4.5. Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. The clinical results do not indicate any interaction of MIRCERA with other medicinal products. The effect of other drugs on the pharmacokinetics and pharmacodynamics of MIRCERA was explored using a population analysis approach. There was no indication of an effect of concomitant medications on the pharmacokinetics and pharmacodynamics of MIRCERA.

4.6. Pregnancy and lactation

Pregnancy:
There are no data from the use of MIRCERA in pregnant woman.
Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal 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.

Lactation:
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 MIRCERA should be made taking into account the benefit of breast-feeding to the child and the benefit of MIRCERA therapy to the woman.

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

The safety data base for MIRCERA from controlled clinical trials comprised 3042 CKD patients where 1939 were treated with MIRCERA and 1103 with an ESA.

Based on the results of 1939 patients, approximately 6 % of patients treated with MIRCERA are expected to experience adverse drug reactions (ADRs). The most frequent reported adverse reaction was hypertension (common)

The frequencies are defined as follows:
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)

Table 2: Adverse reactions attributed to the treatment with MIRCERA in controlled clinical trials in CKD patients

System organ class	**Frequency**	**Adverse reaction**
Nervous system disorders	Uncommon	Headache
Nervous system disorders	Rare	Hypertensive encephalopathy
Skin and subcutaneous tissue disorders	Rare	Rash (maculo-papular, serious)
Injury, poisoning and procedural complications	Uncommon	Vascular access thrombosis
Vascular disorders	Common	Hypertension
Vascular disorders	Rare	Hot flush
Immune system disorders	Rare	Hypersensitivity

All other events attributed to MIRCERA were reported with rare frequency and the majority were mild to moderate in severity. These events were consistent with comorbidities known in the population.

During treatment with MIRCERA, a slight decrease in platelet counts remaining within the normal range was observed in clinical studies. A platelet count below 100 x 10^9/l was observed in 7.5% of patients treated with MIRCERA and 4.4% of patients treated with other ESAs.

Pooled clinical data showed an increase in the incidence of gastrointestinal haemorrhage, with 35 reports associated with Mircera therapy versus 7 reports in the reference epoetin group.

4.9. Post Marketing

Hypersensitivity reactions, including cases of anaphylactic reaction, have been spontaneously reported, frequency unknown.

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

Cases of thrombocytopenia have been spontaneously reported, frequency unknown.

Neutralizing anti-erythropoietin antibody-mediated pure red cell aplasia (AEAB-PRCA) associated with MIRCERA therapy has been reported during post marketing experience (see also section 4.4 Special warnings and precautions for use).

Stevens-Johnson syndrome/ toxic epidermal necrolysis has been reported.

4.10. Overdose

The therapeutic range of MIRCERA 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, MIRCERA should be temporarily withheld (see section 4.2). If clinically indicated, phlebotomy may be performed.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacological Properties

Pharmacotherapeutic group: Blood and blood forming organs, ATC code: B03XA03

MIRCERA is a chemically synthesized continuous erythropoietin receptor activator. Methoxy polyethylene glycolepoetin beta differs from erythropoietin through integration of an amide bond between either the N-terminal amino group or the ε-amino group of lysine, predominantly Lys^{52} and Lys^{45} and methoxy polyethylene glycol succinimidyl butanoic acid. This results in a molecular weight of approximately 60,000 daltons for methoxy polyethylene glycolepoetin beta with the PEG-moiety having an approximate molecular weight of 30,000 daltons.

In contrast with erythropoietin beta, MIRCERA 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. These differential pharmacological properties are relevant in order to achieve a once monthly dosing regimen with MIRCERA in patients.

MIRCERA stimulates erythropoiesis by interaction with the erythropoietin receptor on progenitor cells in the bone marrow. 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.

5.2. Clinical/ Efficacy Studies

Adult Patients

In two randomized controlled studies in CKD patients not on dialysis BA16738 and NH20052, MIRCERA achieved correction of anemia in 97.5 % and 94.1% of patients, respectively. During the first 8 weeks of treatment the proportion of patients experiencing a haemoglobin level greater than 13 g/dL was 11.4 % in the MIRCERA group and 34 % in the darbepoetin alfa group in study BA16738, while the corresponding proportions of patients experiencing a haemoglobin level greater than 12 g/dL were 25.8% in the MIRCERA group and 47.7% in the darbepoetin alfa group in NH20052. In a randomized controlled study in CKD patients on dialysis, MIRCERA achieved correction of anemia in 93.3% of patients.

The median time to response was 43 days in the MIRCERA arm and 29 days in the comparator arm with increases of haemoglobin within the first 6 weeks of 0.2g/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. Patients were randomized to stay on their current treatment or to be converted to MIRCERA in order to achieve stable haemoglobin levels. At the evaluation period (week 29-36), the mean and median level of haemoglobin in patients treated with MIRCERA was virtually identical to their baseline haemoglobin level.

In a controlled, open label, multi-centre study, 490 patients (245 per treatment arm) were randomized to compare the efficacy and safety of MIRCERA with that of darbepoetin alfa for the maintenance treatment of anemia in patients with CKD who are on hemodialysis.

The proportion of responders was significantly higher in patients treated with MIRCERA once-monthly than with darbepoetin alfa once-monthly ($p < 0.0001$). Of the 245 patients in each group, 157 (64.1%) in the MIRCERA group were responders compared to 99 (40.4%) in the darbepoetin alfa group. Response was defined as patients with an average Hb > 10.5 g/dL and an average decrease from individual baseline not exceeding 1.0 g/dL during the evaluation period.

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 systematic review has also been performed involving more than 9,000 cancer patients participating in 57 clinical trials. Meta-analysis of overall survival data produced a hazard ratio point estimate of 1.08 in favour of controls (95% CI: 0.99, 1.18; 42 trials and 8,167 patients). An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6,769 patients) was observed in patients treated with recombinant human erythropoietin. There is therefore consistent evidence to suggest that there may be significant harm to patients with cancer who are treated with recombinant human erythropoietin. The extent to which these outcomes might apply to the administration of recombinant human erythropoietin to patients with cancer, treated with chemotherapy to achieve haemoglobin concentrations less than 13 g/dl, is unclear because few patients with these characteristics were included in the data reviewed.

5.3. Pharmacokinetic properties

The pharmacokinetics of MIRCERA were studied in healthy volunteers and in anaemic patients with CKD including patients on dialysis and not on dialysis.

Following subcutaneous administration of Mircera at 1.2 mcg/kg 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 was 54 %, and the observed terminal elimination half-life was 142 hours.

Following subcutaneous administration of Mircera at 0.8 mcg/kg to CKD patients on peritoneal dialysis, the maximum serum concentrations of methoxy polyethylene glycol-epoetin beta were observed 72 hours (median value) after administration. The absolute bioavailability was 50 – 60 % and the observed terminal elimination half-life was 139 hours in dialysis patients and 142 hours in patients not on dialysis.

Following intravenous administration of Mircera at 0.4 mcg/kg to CKD patients on peritoneal dialysis, the total systemic clearance was 0.494 ml/h per kg. The elimination half-life after intravenous administration of MIRCERA is 134 hours.

A study in 400 CKD patients showed that the volume of distribution of methoxy polyethylene glycol-epoetin beta is approximately 5 L.

A comparison of serum concentrations of MIRCERA 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.

5.4. Pharmacokinetics in special populations

Hepatic Impairment

The pharmacokinetics of MIRCERA are similar in patients with severe hepatic impairment as compared to healthy subjects.

Other special populations

Population analyses evaluated the potential effects of demographic characteristics on the pharmacokinetics of MIRCERA. Results of these analyses showed that no adjustments of the starting dose are necessary for age (>18 years), gender, or race. A population pharmacokinetic analysis also showed no pharmacokinetic differences between patients on dialysis and patients not on dialysis.

5.5. 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 MIRCERA 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 MIRCERA was only observed in target cells (bone marrow progenitor cells).

No significant placental transfer of MIRCERA was observed in the rat and studies in animals have not shown any harmful effect on pregnancy, embryonal/foetal 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 MIRCERA during gestation and lactation were not affected. When MIRCERA 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 PROPERTIES

6.1. Incompatibilities

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

6.2. Shelf life

As stated on the outer carton.

6.3. 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.

For pre-filled syringes: The end-user may remove the medicinal product from refrigeration for storage at 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.

6.4. Special precautions for disposal and other handling

MIRCERA should not be mixed with other products.

MIRCERA is a sterile but unpreserved product. Do not administer more than one dose per pre-filled syringe.

Only solutions which are clear, colourless to slightly yellowish and free of visible particles must be injected.

Do not shake.

Allow the product to reach room temperature before injecting.

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems”, if available in your location.

6.5. Packs

Pre-filled syringe containing 50 µg in 0.3 ml	1
Pre-filled syringe containing 75 µg in 0.3 ml	1
Pre-filled syringe containing 100 µg in 0.3 ml	1

Current at Mar 2019

Medicine: keep out of reach of children

F. Hoffmann-La Roche Ltd,
Basel, Switzerland