MIRCERA®

Methoxy polyethylene glycol-epoetin beta

1. 1. DESCRIPTION

1.1 THERAPEUTIC / PHARMACOLOGIC CLASS OF DRUG

MIRCERA is the first molecule of a new class of Continuous Erythropoietin Receptor Activators called methoxy polyethylene glycol-epoetin beta.

ATC Code – B03XA03

1.2 TYPE OF DOSAGE FORM

Solution for injection supplied as a sterile, ready to use liquid in:

- Single dose pre-filled syringes

1.3 ROUTE OF ADMINISTRATION

Subcutaneous or intravenous.

1.4 STERILE / RADIOACTIVE STATEMENT

Not applicable.

1.5 QUALITATIVE AND QUANTITATIVE COMPOSITION

Single dose pre-filled syringes: containing 50µg, 75µg, 100µg 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 dosage strength in µg indicates the quantity of the protein moiety of the methoxy polyethylene glycol-epoetin beta molecule without consideration of the glycosylation.

The solution is clear and colourless to slightly yellowish.

Excipients: As registered locally.

2. CLINICAL PARTICULARS

2.1 THERAPEUTIC INDICATION(S)

MIRCERA is indicated for the treatment of anaemia associated with chronic kidney disease (CKD) including patients on dialysis and patients not on dialysis.

2.2 DOSAGE AND ADMINISTRATION

Standard dosage

MIRCERA is administered less frequently than other erythropoiesis stimulating agents (ESAs) due to the longer elimination half-life.

Treatment with MIRCERA has to be initiated under the supervision of a healthcare professional.

Treatment of anaemic patients with chronic kidney disease

The solution can be administered subcutaneously (SC) or intravenously (IV), according to clinical preference.

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

It is recommended that haemoglobin is monitored every two weeks until stabilised, 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 currently not treated with an Erythropoiesis Stimulating Agent:

Patients not on dialysis The recommended starting dose 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 body weight may be administered once every two weeks as a single IV or SC injection.

Patients on dialysis –The recommended starting dose of 0.6 microgram/kg body weight may be administered once every two weeks as a single IV or SC injection.

The dose of MIRCERA may be increased by approximately 25 to 50% 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 to 50% 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 levels exceed 12g/dL, the dose is to be reduced by approximately 25 to 50 %.

If the haemoglobin level exceeds 13 g/dL (8.07 mmol/L), therapy is to be interrupted until the haemoglobin level falls below 13 g/dL and then restarted with approximately 50% of the previously administered dose. After dose interruption, a haemoglobin decrease of approximately 0.35 g/dL per week is expected.

Patients treated once every two weeks whose haemoglobin concentration is in the target range may receive MIRCERA administered once monthly using the dose equal to twice the previous once every two weeks dose. Dose adjustments should not be made more often than once a month.

Patients currently treated with an Erythropoiesis Stimulating Agent:

Patients currently treated with an ESA can be converted to MIRCERA administered once a month or, if desired, once every two weeks as a single IV or SC injection. The starting dose of MIRCERA is based on the calculated previously given weekly dose of darbepoetin alfa or epoetin at the time of substitution as described in *Table 1*, below**.** The first injection of MIRCERA should be administered at the next scheduled dose of the previously administered darbepoetin alfa or epoetin.

Table 1. Conversion from Epoetin or Darbepoetin

Previous Weekly Epoetin Dose (Units/week)	Previous Weekly Darbepoetin Alfa Dose (mcg/week)	MIRCERA Dose	
		Once Monthly (mcg/month)	Once Every Two Weeks (mcg/q2w)
<8000	<40	120	60
8000-16000	40-80	200	100
>16000	>80	360	180

If a dose adjustment is required to maintain the target haemoglobin concentration above 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 levels exceed 12g/dL, the dose is to be reduced by approximately 25 to 50%.

If the haemoglobin level exceeds 13 g/dL (8.07 mmol/L), therapy is to be interrupted until the haemoglobin level falls below 13 g/dL and then restarted with approximately

50% of 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 often than once a month.

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 should be administered as soon as possible and administration of MIRCERA is to be restarted at the prescribed dosing frequency.

2.2.1 Special Dosage Instructions

Paediatric use: No dose recommendations can be made for use in patients aged less than 18 years due to the limited data on safety and efficacy (see section 3.1.2 Clinical/Efficacy Studies).

Geriatric use: No adjustment of the starting dose is required in patients aged 65 years or older (see Section 2.5.5 Geriatric Use).

Hepatic Impairment: No adjustments of the starting dose nor dose modification rules are required in patients with any degree of hepatic impairment (see section 3.2.5, Pharmacokinetics in Special Populations).

2.3 CONTRAINDICATIONS

MIRCERA is contraindicated in patients with:

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

2.4 WARNINGS AND PRECAUTIONS

2.4.1 General

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.

Lack of effect: The most common reasons for incomplete response to ESAs are iron deficiency and inflammatory disorders. The following conditions may also compromise

the effectiveness of ESAs therapy: chronic blood loss, bone marrow fibrosis, severe aluminium overload due to treatment of renal failure, folic acid or vitamin B_{12} deficiencies, and haemolysis. 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. If 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.

Blood pressure monitoring: As with other ESAs, blood pressure may rise during treatment of anemia with MIRCERA. Blood pressure should be adequately controlled before, at initiation of and during treatment with MIRCERA. If high blood pressure is difficult to control by drug treatment or dietary measures, the dose of MIRCERA must be reduced or withheld (see 2.2, Dosage and Administration).

Effect on tumor 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 tumor 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.

The safety and efficacy of MIRCERA therapy has not been established in patients with haemoglobinopathies, seizures or with a platelet level greater than 500 x 10^9/L. Therefore, caution should be used in these patients.

2.4.2 Drug Abuse and Dependence

Misuse by non-anaemic persons may lead to an excessive increase in Hb. This may be associated with life threatening complications of the cardiovascular system.

2.4.3 Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed. However, no effects are expected based on the mechanism of action and the known safety profile of MIRCERA.

2.4.4 Laboratory Tests

No data to report.

2.4.5 Interactions 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.

2.5 USE IN SPECIAL POPULATIONS

2.5.1 Pregnancy

There are no adequate data on the use of MIRCERA in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.

Caution should be exercised when prescribing MIRCERA to pregnant women.

2.5.2 Labor and Delivery

No data to report.

2.5.3 Nursing Mothers

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 breastfeeding to the child and the benefit of MIRCERA therapy to the woman.

2.5.4 Paediatric Use

No dose recommendations can be made for use in patients aged less than 18 years due to the limited data on safety and efficacy (see section 3.1.2 Clinical/Efficacy Studies).

2.5.5 Geriatric Use

Of the 1789 MIRCERA-treated CKD patients in Phase II and Phase III clinical studies of MIRCERA, 24% were age 65 to 74 years, while 20% were age 75 years and over. Based on population analyses, no adjustment of the starting dose is required in patients aged 65 years or older. See section 2.2.1 Special Dosage Instructions.

2.5.6 Renal Impairment

No data to report.

2.5.7 Hepatic Impairment

No data to report.

2.6 UNDESIRABLE EFFECTS

2.6.1 Clinical Trials

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 following descriptors are used to describe the frequency of ADRs attributed to treatment with MIRCERA in controlled clinical trials: Common (≥1/100 and <1/10), Uncommon (≥1/1000 and <1/100), and Rare (≥1/10,000 and <1/1000).

Table 3: Adverse drug reactions attributed to the treatment with MIRCERA in controlled clinical trials in CKD patients.

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

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

2.6.1.1 Laboratory Abnormalities

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.

2.6.2 Post Marketing

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 2.4 General Warnings and Precautions).

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

2.6.3 Laboratory Abnormalities

See section 2.6.2 Post Marketing.

2.7 OVERDOSE

The therapeutic range of MIRCERA is wide and individual response to therapy must be considered when MIRCERA 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 2.2, Dosage and Administration). If clinically indicated, phlebotomy may be performed.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 PHARMACODYNAMIC PROPERTIES

MIRCERA is a chemically synthesized continuous erythropoietin receptor activator. Methoxy polyethylene glycol-epoetin 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 butanoic acid. This results in a molecular weight of approximately 60,000 daltons for methoxy polyethylene glycol-epoetin beta with the PEG-moiety having an approximate molecular weight of 30,000 daltons.

In contrast with erythropoietin, 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.

3.1.1 Mechanism of Action

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.

3.1.2 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.

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 to 36), the mean and median level of haemoglobin in patients treated with MIRCERA was virtually identical to the 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.

Paediatric Patients

A phase II, dose-finding, open-label, multiple dose, multicenter study was conducted in 64 paediatric patients (aged 5-17 years old) with CKD who were on hemodialysis, to determine the effective starting dose of MIRCERA IV when switching from maintenance treatment with another ESA (epoetin alfa/beta or darbepoetin alfa). The primary efficacy endpoint in this study (change in Hb concentration (g/dL) between the baseline and evaluation periods) has been met. Overall, the adverse event profile observed was consistent with the safety profile in adults.

3.2 PHARMACOKINETIC PROPERTIES

In patients, the pharmacokinetic and the pharmacologic properties allow monthly administration of MIRCERA due to the long elimination half-life. The elimination half-

life after IV administration of MIRCERA is 15 to 20 times longer compared to recombinant human erythropoietin.

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

In CKD patients, clearance and volume of distribution of methoxy polyethylene glycol-epoetin beta were not dose dependent.

In CKD patients, the pharmacokinetics of MIRCERA were studied after the first dose and after administrations on week 9 and on week 19 or 21. Multiple dosing had no effect on clearance, volume of distribution and bioavailability of methoxy polyethylene glycol-epoetin beta. After administration every 4 weeks in CKD patients, there was no meaningful accumulation of methoxy polyethylene glycol-epoetin beta, as demonstrated by a ratio of accumulation of 1.03. After administration every 2 weeks, the ratio of accumulation was 1.12.

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 methoxy polyethylene glycol-epoetin beta.

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

The results of a study in 42 healthy volunteers indicated that the site of subcutaneous injection (abdomen, arm or thigh) has no clinically relevant effect on the pharmacokinetics, pharmacodynamics or local tolerability of MIRCERA. Based on these results, all three sites are considered suitable for subcutaneous injection with MIRCERA.

3.2.1 Absorption

Absorption after subcutaneous administration

Following SC administration to CKD patients, the maximum serum concentrations of methoxy polyethylene glycol-epoetin beta were observed 72 hours (median value) after administration in dialysis patients and 95 hours after administration in patients not on dialysis.

The absolute bioavailability of methoxy polyethylene glycol-epoetin beta after SC administration was 62% and 54%, in dialysis patients and patients not on dialysis, respectively.

3.2.2 Distribution

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

3.2.3 Metabolism

No data to report.

3.2.4 Elimination

Following IV administration to CKD patients, the $t_{1/2}$ for methoxy polyethylene glycol-epoetin beta was 134 hours [or 5.6 days], and the total systemic clearance was 0.494 mL/h per kg. Following SC administration the observed terminal elimination half-life ($t_{1/2}$) was 139 hours in dialysis patients and 142 hours in patients not on dialysis.

3.2.5 Pharmacokinetics in Special Populations

Hepatic Impairment

The pharmacokinetics of MIRCERA are similar in patients with severe hepatic impairment as compared to healthy subjects (see section 2.2.1 Special Dosage Instructions).

Paediatric Population

The pharmacokinetics of MIRCERA were studied in 64 paediatric CKD patients (aged 5-17 years old) receiving hemodialysis. At steady state (following the third IV administration of MIRCERA) the maximum observed exposures were a geometric mean C_{max} of 66.1 ng/mL and a geometric mean $AUC_{0\text{-}tau}$ of 7170 ng.hr/mL. Subsequently, Mircera serum concentrations declined with an apparent mean half-life of approximately 121 to 147 hours (geometric mean) comparable to adults.

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.

3.3 PRECLINICAL SAFETY

3.3.1 Carcinogenicity

The carcinogenic potential of MIRCERA has not been evaluated in long-term animal studies. MIRCERA 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).

3.3.2 Mutagenicity

No data to report.

3.3.3 Impairment of Fertility

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.

3.3.4 Teratogenicity

Studies in animals have not shown any harmful effect of MIRCERA on pregnancy, embryonal/foetal development, parturition or postnatal development.

3.3.5 Other

No data to report.

4. PHARMACEUTICAL PARTICULARS

4.1 STORAGE

This medicine should not be used after the expiry date (EXP) shown on the pack.

Store in the refrigerator at 2°C to 8°C.

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

Do not freeze.

For countries in climatic zones I and II (WHO climatic zones I to IV), the following storage conditions apply:

For pre-filled syringes: The patient may remove the 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 product must be used within this period.

4.2 SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL

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 or vial.

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.

4.3 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

Medicine: keep out of reach of children

Current at March 2020

Made in Switzerland by F. Hoffmann-La Roche Ltd, Basel, Switzerland,

Manufacturing site Kaiseraugst, Switzerland & Roche Diagnostics GmbH, Mannheim, Germany