Mircera®

Methoxy polyethylene glycol-epoetin beta

Composition

Active substance: methoxy polyethylene glycol-epoetin beta (produced by recombinant DNA technology in Chinese hamster ovary [CHO] cells)

Excipients: sodium dihydrogen phosphate, sodium sulphate, mannitol, methionine, poloxamer 188, water for injection

Pharmaceutical form and quantity of active substance per unit

MIRCERA 30 µg/0.3 ml solution for injection in a prefilled syringe

Each prefilled syringe with ready-to-use solution for injection contains 30 µg methoxy polyethylene glycol-epoetin beta.

Excipients sufficient for 0.3 ml of solution.

MIRCERA 50 µg/0.3 ml solution for injection in a prefilled syringe

Each prefilled syringe with ready-to-use solution for injection contains 50 µg methoxy polyethylene glycol-epoetin beta.

Excipients sufficient for 0.3 ml of solution.

MIRCERA 75 µg/0.3 ml solution for injection in a prefilled syringe

Each prefilled syringe with ready-to-use solution for injection contains 75 µg methoxy polyethylene glycol-epoetin beta.

Excipients sufficient for 0.3 ml of solution.

MIRCERA 100 µg/0.3 ml solution for injection in a prefilled syringe

Each prefilled syringe with ready-to-use solution for injection contains 100 µg methoxy polyethylene glycol-epoetin beta.

Excipients sufficient for 0.3 ml of solution.

MIRCERA 120 µg/0.3 ml solution for injection in a prefilled syringe

Each prefilled syringe with ready-to-use solution for injection contains 120 µg methoxy polyethylene glycol-epoetin beta.

Excipients sufficient for 0.3 ml of solution.

MIRCERA 150 µg/0.3 ml solution for injection in a prefilled syringe

Each prefilled syringe with ready-to-use solution for injection contains 150 µg methoxy polyethylene glycol-epoetin beta.

Excipients sufficient for 0.3 ml of solution.

MIRCERA 200 µg/0.3 ml solution for injection in a prefilled syringe

Each prefilled syringe with ready-to-use solution for injection contains 200 µg methoxy polyethylene glycol-epoetin beta.

Excipients sufficient for 0.3 ml of solution.

MIRCERA 250 µg/0.3 ml solution for injection in a prefilled syringe

Each prefilled syringe with ready-to-use solution for injection contains 250 µg methoxy polyethylene glycol-epoetin beta.

Excipients sufficient for 0.3 ml of solution.

MIRCERA 360 µg/0.6 ml solution for injection in a prefilled syringe

Each prefilled syringe with ready-to-use solution for injection contains 360 µg methoxy polyethylene glycol-epoetin beta.

Excipients sufficient for 0.6 ml of solution.

The dosage given in µg refers to the protein moiety of the methoxy polyethylene glycol-epoetin beta molecule without taking glycosylation into account.

MIRCERA is a clear, colourless to pale yellow solution.

Indications and potential uses

Treatment of symptomatic renal anemia associated with chronic kidney disease (CKD) in dialysed or non-dialysed adult patients.

The safety and efficacy of MIRCERA therapy have not been established in other indications.

Dosage and administration

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

Treatment of symptomatic anemia in CKD patients

Anemia symptoms and sequelae may vary with age, gender and overall disease severity; evaluation of the individual patient's clinical course and condition by a physician is therefore necessary. MIRCERA should be administered either subcutaneously or intravenously to increase hemoglobin to no higher than 12 g/dl (7.45 mmol/l). In patients not receiving hemodialysis, subcutaneous use is preferable to avoid puncturing peripheral veins.

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

Because of intraindividual variations between patients, hemoglobin values above or below the desired level may occasionally be observed. Such hemoglobin variations can be offset by dose adjustment, taking account of the hemoglobin target range of 10 g/dl (6.21 mmol/l) to 12 g/dl (7.45 mmol/l). A sustained hemoglobin level of greater than 12 g/dl (7.45 mmol/l) should be avoided; guidelines for appropriate dose adjustment when hemoglobin values exceed 12 g/dl (7.45 mmol/l) are described below.

A rise in hemoglobin of greater than 2 g/dl (1.24 mmol/l) over a four-week period should be avoided. If it occurs, appropriate dose adjustment should be undertaken as specified.

Patients should be monitored closely to ensure use of the lowest approved dose of MIRCERA that adequately controls the symptoms of anemia.

It is recommended that hemoglobin levels be monitored every two weeks until stabilised and at regular intervals thereafter.

Patients not currently treated with an erythropoiesis--stimulating agent (ESA):

Patients not on dialysis – To increase the hemoglobin level to values exceeding 10 g/dl (6.21 mmol/l), the recommended starting dose is 1.2 µg/kg body weight administered once monthly as a single subcutaneous injection. Alternatively a starting dose of 0.6 µg/kg body weight can be administered once every two weeks as a single i.v. or s.c. injection.

Patients on dialysis – To increase the hemoglobin level to values exceeding 10 g/dl (6.21 mmol/l), a starting dose of 0.6 µg/kg body weight can be administered once every two weeks as a single i.v. or s.c. injection.

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

If the rise in hemoglobin exceeds 2 g/dl (1.24 mmol/l) in one month or if the hemoglobin level is increasing and approaching 12 g/dl (7.45 mmol/l), the dose should be reduced by approximately 25%. If the hemoglobin 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. A hemoglobin decrease of approximately 0.35 g/dl (0.22 mmol/l) per week is expected after treatment interruption. Dose adjustments should not be made more than once a month.

In patients treated once every two weeks whose hemoglobin concentration exceeds 10 g/dl (6.21 mmol/l), MIRCERA can be administered once monthly at double the dose previously administered once every two weeks.

Patients currently treated with an erythropoiesis--stimulating agent (ESA):

In patients currently treated with an ESA, MIRCERA can be administered once a month as a single intravenous or subcutaneous injection. The starting dose of MIRCERA is calculated on the basis of the weekly ESA dose previously administered at the time of the treatment switch, as described in Table 1. The first injection should start on the date scheduled in the previous administration regime comprising darbepoetin alfa or epoetin.

Table 1. MIRCERA starting doses

Previous weekly darbepoetin alfa i.v. or s.c. dose (µg/week)	Previous weekly epoetin i.v. or s.c. dose (IU/week)	Monthly MIRCERA i.v. or s.c. dose (µg/once monthly)
<40	<8000	**120**
40–80	8000–16,000	**200**
>80	>16,000	**360**

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

If the rise in hemoglobin levels exceeds 2 g/dl (1.24 mmol/l) in one month or if the hemoglobin level is increasing and approaching 12 g/dl (7.45 mmol/l), the dose should be reduced by approximately 25%. If the hemoglobin 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. A hemoglobin decrease of approximately 0.35 g/dl (0.22 mmol/l) per week is expected after treatment interruption. Dose adjustments should not be made more than once a month.

Missed dose

If a dose of MIRCERA is missed, the missed dose should be administered as soon as possible and treatment with MIRCERA continued at the prescribed dosing frequency.

Use in children

In the absence of safety and efficacy data, MIRCERA is not recommended for use in children and adolescents under 18 years of age.

Use in the elderly

In clinical studies, 24% of patients treated with MIRCERA were 65 to 74 years old and 20% were 75 years or older. No dose adjustment is necessary in patients aged ≥65 years.

Use in patients with hepatic impairment

No adjustment of the starting dose and no dosage adjustment rule are necessary in patients with hepatic impairment, regardless of its severity (see *Pharmacokinetics in special patient groups*).

Contraindications

Hypersensitivity to the active substance or any of the constituent excipients.

MIRCERA must not be used in patients with untreated or poorly controllable hypertension.

Warnings and precautions

Hemoglobin levels exceeding 12 g/dl may increase the risk of cardiovascular events, including death. Controlled clinical studies have shown no benefit of ESA use when the hemoglobin level is higher than that necessary to control symptoms of anemia and avoid blood transfusion.

Iron supplementation

Supplemental iron therapy is recommended for all patients with serum ferritin levels below 100 µg/l or a transferrin saturation index below 20%. To ensure effective erythropoiesis, iron status must be checked in all patients before and during treatment.

Failure to respond to MIRCERA therapy should prompt an immediate search for causative factors.

Deficiencies of iron, folic acid or vitamin B_{12} reduce the efficacy of ESAs and should therefore be corrected. Intercurrent infections, inflammatory or traumatic episodes, occult blood loss, hemolysis, severe aluminium toxicity, underlying hematological disease or myelofibrosis may also compromise the erythropoietic response. A reticulocyte count should be considered part of the bone marrow work-up.

If all the conditions mentioned have been excluded and the patient has a sudden drop of hemoglobin associated with reticulocytopenia and anti-erythropoietin antibodies, bone marrow examination for erythroblastopenia (pure red cell aplasia [PRCA]) should be considered. If PRCA is diagnosed, it is mandatory to discontinue MIRCERA administration and withhold all other ESAs.

Erythroblastopenia (PRCA)

Cases of erythroblastopenia due to anti-erythropoietin antibodies have been reported during treatment with ESAs, including MIRCERA. These antibodies cross-react with other ESAs, and MIRCERA treatment must not be started in patients in whom the presence of antibodies is suspected or confirmed.

Blood pressure monitoring

As with other ESAs, blood pressure may rise during treatment with MIRCERA. Blood pressure should be properly controlled in all patients at the initiation of and during treatment with MIRCERA. If hypertension is difficult to control by medication or diet, MIRCERA must be reduced in dose or withheld (see *Contraindications*).

Effect on tumor growth

MIRCERA, like other ESAs, is a growth factor that primarily stimulates erythrocyte 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 certain types of malignancy. MIRCERA is not approved for the treatment of anemia in cancer patients.

Other

The safety and efficacy of MIRCERA have not been established in patients with hemoglobinopathies, seizure disorders, bleeding or a recent history of bleeding requiring transfusions or with platelet counts exceeding 500×10^9/l. Caution is therefore required in such patients.

Misuse

Misuse of MIRCERA by healthy people (e.g. for doping) may lead to an excessive increase in hemoglobin levels. This carries a risk of life-threatening cardiovascular complications (risk of thrombosis due to hemoconcentration in erythrocytosis).

Hemoglobin concentration: in CKD patients the maintenance hemoglobin concentration should not persistently exceed the upper limit of the target hemoglobin concentration recommended under *Dosage and administration*. In clinical trials an increased risk of death and serious cardiovascular events was observed when ESAs were used to achieve a target hemoglobin level exceeding 12 g/dl (7.5 mmol/l).

Controlled clinical trials have not shown significant benefits attributable to the administration of epoetins when the hemoglobin concentration is increased beyond the level necessary to control symptoms of anemia and avoid blood transfusion.

Interactions

No interaction studies have been performed. Clinical studies have produced no evidence that MIRCERA interacts with other therapeutic agents. The effects of other drugs on the pharmacokinetics and pharmacodynamics of MIRCERA were investigated in a population analysis. No evidence was found of an effect on the pharmacokinetics and pharmacodynamics of MIRCERA.

Pregnancy and lactation

Pregnancy

There are insufficient data on use of MIRCERA in pregnant women.

Animal studies have shown no direct adverse effects on pregnancy, embryofetal development or delivery (see *Preclinical data*). Caution is required when prescribing MIRCERA 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. In deciding whether to continue or discontinue breastfeeding or MIRCERA therapy, the benefit of breastfeeding to the child should be weighed against the benefit of MIRCERA to the mother.

Effects on ability to drive and operate machinery

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

Undesirable effects

Clinical-trial experience

The safety data come from clinical trials that included 3042 CKD patients, 1939 of whom were treated with MIRCERA and 1103 with another ESA. Undesirable effects must be expected in some 6% of patients treated with MIRCERA. The most frequently reported undesirable effect was hypertension (common).

Table 2. Undesirable effects attributed to MIRCERA treatment in controlled clinical trials in CKD patients

Organ class	Frequency	Adverse reaction
Vascular	Common	Hypertension
Administration site reactions	Uncommon	Vascular-access thrombosis
Nervous system	Occasional Rare	Headache Hypertensive encephalopathy
Skin	Rare	Rash (maculopapular, severe)
Immune system	Rare	Hypersensitivity

All the other events attributed to MIRCERA were rare and in most cases mild to moderate in severity. These events coincided with the comorbidities documented in the population concerned.

A slight decrease in platelet count remaining within the normal range was observed on MIRCERA therapy in the clinical studies.

Platelet counts below 100×10^9/l were observed in 7.5% of patients treated with MIRCERA and in 4.4% of those receiving another ESA.

Post-marketing phase

Neutralizing anti-erythropoietin antibody-mediated pure red cell aplasia (AEAB-PRCA) associated with MIRCERA therapy has been reported (see also section ~~2.4 *General* *Warnings and p*~~*P*~~*r*~~*recautions*). With this exception, the safety data collected during post-~~-~~marketing experience reflects the expected adverse-event profile in these populations as well as the pharmacological

adverse-event profile of MIRCERA (see *Warnings and precautions*, *Dosage and administration*, and *Undesirable effects – Clinical-trial experience*).

Overdosage

MIRCERA has a wide therapeutic range. Individual response must be considered when starting treatment. Overdose can cause signs due to an exaggerated pharmacodynamic effect, for example excessive erythropoiesis. If hemoglobin levels are too high, MIRCERA therapy should be temporarily withheld (see *Dosage and administration*). If clinically indicated, phlebotomy may be performed.

Properties and effects

ATC code: B03XA03

Mechanism of action and pharmacodynamics

Methoxy polyethylene glycol-epoetin beta, the active substance of MIRCERA, is a continuous erythropoietin receptor activator that differs from erythropoietin in its activity at the receptor level, which is characterised by slower association with and faster dissociation from the receptor, reduced specific activity in vitro with increased activity in vivo, and a longer half-life. Its average molecular weight is about 60 kDa, of which the protein portion plus the carbohydrate accounts for approximately 30 kDa.

MIRCERA stimulates erythropoiesis by interacting with the erythropoietin receptor on the surface of progenitor cells in the bone marrow. As the primary growth factor for erythrocyte development, the natural hormone erythropoietin is produced by the kidney and released into the bloodstream in response to the level of tissue oxygen saturation. In hypoxia, it interacts with erythroid progenitor cells to increase the production of erythrocytes.

In two randomised controlled studies in patients with chronic renal disease not on dialysis, BA16738 and NH20052, MIRCERA corrected anemia in 97.5% and 94.1% of the patients, respectively. In study BA16738, the proportion of patients with a hemoglobin level exceeding 13 g/dl in the first 8 treatment weeks was 11.4% in the MIRCERA group and 34% in the darboetin alfa group. In study NH20052, the proportion of patients with a hemoglobin level exceeding 12 g/dl was 25.8% in the MIRCERA group and 47.7% in the darboetin alfa group. In the randomised controlled study in chronic renal failure with dialysis, MIRCERA corrected anemia in 93.3% of patients.

Four randomised controlled studies were performed in dialysis patients currently treated with ESAs. Patients were randomised to stay on their current treatment or be switched to MIRCERA in order to achieve stable hemoglobin levels. In the evaluation period (weeks 29–36), mean and median hemoglobin levels in patients in the MIRCERA group were virtually identical to their baseline levels.

In a randomised study of epoetin beta in predialysis patients (CREATE), in which 603 patients with renal anemia were assigned to a group with either high (13–15 g/dl) or low (10.5–11.5 g/dl) target hemoglobin levels, the frequency of cardiovascular events in the group with higher hemoglobin levels was 19% vs 16% in the lower target hemoglobin group (58 vs 47 cases; p=0.20). The frequency of thromboembolic events in this study was 11% in the high target hemoglobin group and 7% in that with a low target hemoglobin as the treatment goal (p=0.06). As reported earlier, the frequency of vascular access thrombosis in patients referred for dialysis was likewise higher in those with a high hemoglobin level as the treatment goal (4% vs 3%; p=0.42).

In a randomised study of epoetin alfa in predialysis patients (CHOIR), in which 1432 patients were assigned to a study arm with a high target hemoglobin level (13.5 g/dl) or one with a low target hemoglobin level (11.5 g/dl), there were significantly more cardiovascular events in the high target hemoglobin group than in the group with low target hemoglobin levels (17% vs 14%; 125 vs 97 cases; p=0.03). The frequency of thromboembolic events in the high hemoglobin study arm was 18% vs 17% in the low hemoglobin arm (p=0.65).

In the MIRCERA development programme, no study was performed to compare high and low target hemoglobin levels in a similar patient population.

Pharmacokinetics

The pharmacokinetic and pharmacological properties of MIRCERA make it possible to treat patients with a once-monthly regimen, thanks to its long elimination half-life. After intravenous dosing, MIRCERA has an elimination half-life 15 to 20 times longer than that of recombinant human erythropoietin.

The pharmacokinetics of MIRCERA were studied in healthy volunteers and in anemic dialysed and non-dialysed CKD patients.

The clearance and volume of distribution of MIRCERA in the CKD patients were not dose-dependent.

MIRCERA pharmacokinetics were studied in CKD patients after the first dose and after dosing in weeks 9 and 19 or 21. Repeated administration had no effects on the clearance, volume of distribution or bioavailability of MIRCERA. Four-weekly administration in CKD patients led to virtually no accumulation of MIRCERA, as shown by the accumulation ratio of 1.03. After 2-weekly administration the accumulation ratio was 1.12.

Comparison of MIRCERA serum concentrations measured before and after hemodialysis in 41 CKD patients showed that hemodialysis had no effect on the drug's pharmacokinetics.

An analysis in 126 CKD patients showed no pharmacokinetic difference between dialysed and non-dialysed patients.

Absorption

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

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

Distribution

A study in 400 CKD patients showed that MIRCERA has a volume of distribution of approximately 5 l.

Elimination

Following intravenous administration to CKD patients, the half-life of MIRCERA was 134 hours (5.6 days) and the total systemic clearance was 0.494 ml/h per kg. Following subcutaneous administration, the elimination half-life was 139 hours (5.8 days) in CKD patients on dialysis and 142 hours in patients not on dialysis.

Pharmacokinetics in special patient groups

Patients with hepatic impairment

In patients with severe hepatic impairment, the pharmacokinetics of MIRCERA are similar to those in healthy subjects (see *Dosage and administration*).

Other special populations

Population analyses have provided no evidence that pharmacokinetics are markedly influenced by age, gender or ethnicity. Another population-based pharmacokinetic analysis also failed to reveal major differences in pharmacokinetics between dialysed and non-dialysed patients.

Preclinical data

Preclinical data based on conventional studies of cardiovascular safety pharmacology, repeated-dose toxicity, reproductive toxicity and carcinogenic potential show no special hazard for humans.

The carcinogenic potential of MIRCERA has not been evaluated in long-term animal studies. MIRCERA did not induce a proliferative response in non-hematological tumor cell lines in vitro. In a six-month rat toxicity study, no mitogenic or tumorigenic responses were observed in non-hematological tissues. In addition, in a panel of human tissues, in vitro binding of MIRCERA was only observed in target cells (bone marrow progenitor cells).

Animal studies produced no evidence of adverse effects on pregnancy, embryofetal development or delivery. Peri-postnatal studies showed reduced weight gain in neonates. Subcutaneous administration of MIRCERA to male and female rats before and during mating had no effect on reproductive performance, fertility or sperm parameters.

Additional information

Incompatibilities

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

Stability

This medicinal product must not be used after the expiry date (EXP) shown on the pack.

Special precautions for storage

Store in a refrigerator (2-8°C).

Do not freeze.

Keep prefilled syringe in the original carton, protected from light.

Prefilled syringe

The patient can store the product outside the refrigerator at room temperature (up to 25°C) on one occasion for up to 1 month. Once removed from the refrigerator, the product must be used within this period.

Instructions for handling

The MIRCERA prefilled syringe is ready for use. The prefilled syringe contains no preservatives and is intended for a single injection only. Only one dose should be administered per syringe. Only solutions that are clear, colourless to pale yellow and free of visible particles may be injected.

Do not shake.

Allow the prefilled syringe to reach room temperature before injecting.
Dispose of any unused product or waste in accordance with local requirements.

Packs

Prefilled syringe containing 30 µg in 0.3 ml:	1
Prefilled syringe containing 50 µg in 0.3 ml:	1
Prefilled syringe containing 75 µg in 0.3 ml:	1
Prefilled syringe containing 100 µg in 0.3 ml:	1
Prefilled syringe containing 120 µg in 0.3 ml:	1
Prefilled syringe containing 150 µg in 0.3 ml:	1
Prefilled syringe containing 200 µg in 0.3 ml:	1
Prefilled syringe containing 250 µg in 0.3 ml:	1
Prefilled syringe containing 360 µg in 0.6 ml:	1

This is a medicament

A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

The doctor and the pharmacist are experts in medicine, its benefits and risks.

Do not by yourself interrupt the period of treatment prescribed for you.

Do not repeat the same prescription without consulting your doctor.

Medicine: keep out of reach of children

Council of Arab Health Ministers

Union of Arab Pharmacists

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