

1. NAME OF THE MEDICINAL PRODUCT

MIRCERA 400 micrograms/0.6 ml solution for injection in pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

0.6 ml (one pre-filled syringe) contains 400 micrograms of methoxy polyethylene glycol-epoetin beta*. The strength indicates the quantity of the protein moiety of the methoxy polyethylene glycol-epoetin beta molecule without consideration of the glycosylation.

*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.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe.
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).
The safety and efficacy of MIRCERA therapy in other indications has not been established.

4.2 Posology and method of administration

Treatment of symptomatic anaemia in adult chronic kidney disease patients

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

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

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) 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 dose of MIRCERA is used to provide adequate control of the symptoms of anaemia.

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

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 in order to increase the haemoglobin to greater than 10 g/dl (6.21 mmol/l).

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 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 (0.22 mmol/l) per week is expected. Dose adjustments should not be made more frequently than once a month.

If the haemoglobin concentration above 10 g/dl (6.21 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

| Previous weekly darbepoetin alfa intravenous or subcutaneous dose (microgram/week) | Previous weekly epoetin intravenous or subcutaneous dose (IU/week) | Monthly MIRCERA intravenous or subcutaneous dose (microgram/once monthly) |
|---|---|--|
| <40 | <8000 | 120 |
| 40-80 | 8000-16000 | 200 |
| >80 | >16000 | 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 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 (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 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.

Elderly patients

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 of the dose modification rules are required in hepatic impaired patients (see section 5.2).

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 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 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.

Pure Red Cell Aplasia caused by anti-erythropoietin antibodies has been reported in association with ESAs. 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.

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 and serious cardiovascular events was observed when erythropoiesis stimulating agents (ESAs) were administered to target a haemoglobin of greater than 12g/dl (7.5 mmol/l).

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. 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.

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 $500 \times 10^9/l$. 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.

Excipients: This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. 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 MIRCERA alters the metabolism of other medicinal products.

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 from clinical trials comprised 2737 CKD patients, including 1789 patients treated with MIRCERA and 948 with an ESA. Approximately 6% of patients treated with MIRCERA are expected to experience adverse reactions. 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

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.

Platelet counts below $100 \times 10^9/l$ were observed in 7% of patients treated with MIRCERA and 4% of patients treated with ESAs.

4.9 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 Pharmacodynamic properties

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

Methoxy polyethylene glycol-epoetin beta, the active ingredient 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.

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.

Data from correction studies show that the Hb response rates in the MIRCERA group at the end of the correction period were high (93.3% and 97.5% in the studies in patients on dialysis and not on dialysis respectively) and comparable to comparators (91.3% and 96.3%, respectively). 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 0.2 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. 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.

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 2833 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 9000 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 8167 patients). An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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.

5.2 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 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 MIRCERA is 134 hours.

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.

In a single dose study, after IV administration, the pharmacokinetics of MIRCERA are similar in patients with severe hepatic impairment as compared to healthy subject (see section 4.2).

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 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 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, MIRCERA should not be mixed with other medicinal products.

6.3 Shelf life

2 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 room temperature (not above 25°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 material) and tip cap (bromobutyl rubber material) with needle 27G1/2. Each pre-filled syringe contains 0.6 ml solution for injection and comes in a pack size of 1.

6.6 Special precautions for disposal and other handling

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. 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 Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/400/014

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 July 2007

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) <http://www.emea.europa.eu/>