Mircera®

Methoxy polyethylene glycol-epoetin beta ρ

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 50 μg, 75 μg, 100 μg, 120 μg, 150 μg or 200 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 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 colorless to slightly yellowish.
Excipients: sodium phosphate monobasic monohydrate, sodium sulphate, mannitol, methionine, poloxamer 188 and water for injections.

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

MIRCERA is indicated for the treatment of anemia associated with chronic kidney disease (CKD) including patients on dialysis and patients not on dialysis. The safety and efficacy of MIRCERA therapy in other indications has not been established.

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 anemic 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 hemoglobin 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 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 hemoglobin 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 hemoglobin level is obtained.
If the rate of rise in hemoglobin 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 hemoglobin level exceeds 13 g/dL (8.07 mmol/L), therapy is to be interrupted until the hemoglobin level falls below 13 g/dl and then restarted with approximately 50% of the previously administered dose. After dose interruption a hemoglobin 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 hemoglobin concentration above 10 g/dl, the monthly dose may be adjusted by approximately 25%.

If the rate of rise in hemoglobin 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 hemoglobin level exceeds 13 g/dL (8.07 mmol/L), therapy is to be interrupted until the hemoglobin level falls below 13 g/dL and then restarted with approximately 50% of the previously administered dose. After dose interruption a hemoglobin 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

Pediatric 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 2.5.3 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 B12 deficiencies, and hemolysis. If all the conditions mentioned are excluded and the patient has a sudden drop of hemoglobin 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 hemoglobinopathies, seizures or with a platelet level greater than 500 x 10^9/l. Therefore, caution should be used in these patients.
Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported in association with epoetin treatment. More severe cases have been observed with long-acting epoetins. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, Mircera should be withdrawn immediately and an alternative treatment considered. If the patient has developed a severe cutaneous skin reaction such as SJS or TEN due to the use of Mircera, treatment with Mircera must not be restarted in this patient at any time.

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/fetal 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 Pediatric 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

See sections 2.2.1 Special Dosage Instructions and 3.2.5 Pharmacokinetics in Special Populations.

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

System organ class	Frequency	Adverse reaction
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-erythropoetin 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.

2.6.2.1 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 hemoglobin 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 hemoglobin 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 hemoglobin levels. At the evaluation period (week 29 to 36), the mean and median level of hemoglobin in patients treated with MIRCERA was virtually identical to the baseline hemoglobin 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 hemodialysis in 41 CKD patients showed that hemodialysis 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 s.c. 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 Cmax of 66.1 ng/mL and a geometric mean AUC0-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-hematological tumor cell lines *in vitro*. In a six-month rat toxicity study no tumorigenic or unexpected mitogenic responses were observed in non-hematological 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/fetal development, parturition or postnatal development.

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 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.
Only solutions which are clear, colorless to slightly yellowish and free of visible particles must be injected.
Do not shake.
Allow the product to reach room temperature before injecting.
(See instructions at the end of this leaflet)
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
Pre-filled syringe containing 120 µg in 0.3 ml	1
Pre-filled syringe containing 150 µg in 0.3 ml	1
Pre-filled syringe containing 200 µg in 0.3 ml	1

Medicine: keep out of reach of children

MYPIMircera20211203/CDS11.0
Date of revision: 3 December 2021

ρ
Pre-filled syringes:
Made for F. Hoffmann-La Roche Ltd, Basel, Switzerland
by F. Hoffmann-La Roche Ltd., Wurmisweg 4303 Kaiseraugst, Switzerland
and
Release of finished drug product
by Roche Diagnostics GmbH, Sandhofer Strasse 16, 68305 Mannheim, Germany

MIRCERA pre-filled syringe
Instructions For Use

The following instructions explain how to use the MIRCERA pre-filled syringe to give yourself or another individual an injection.
It is important to read and follow these instructions carefully so that you are able to use the pre-filled syringe correctly and safely.
Do not attempt to administer an injection until you are sure that you understand how to use the pre-filled syringe, if in doubt contact a healthcare professional.
Always follow all directions in these Instructions for Use as they may differ from your experience. These instructions will allow preventing incorrect treatments or risks such as needle stick injury or an early activation of the needle safety device, or problems related to the attachment of the needle.

IMPORTANT INFORMATION

- Only use MIRCERA pre-filled syringe if you have been prescribed this medication.
- Read the packaging and ensure you have the dose prescribed by your healthcare professional.
- **Do not** use MIRCERA if the syringe, the box or the plastic tray containing the syringe appears to be damaged.
- **Do not** touch the activation guards (see Figure A) as this may damage the syringe and make it unusable.
- **Do not** use the syringe if the contents are cloudy, hazy or contain particles.
- Never attempt to take the syringe apart.
- Never handle or pull on the syringe by its plunger.
- **Do not** remove the needle shield until you are ready to perform an injection.
- **Do not** swallow the medicine in the syringe.
- **Do not** inject through clothing.
- Never re-use a syringe.

STORAGE

Keep the pre-filled syringe and the puncture-resistant/ sharps container out of the reach of children.

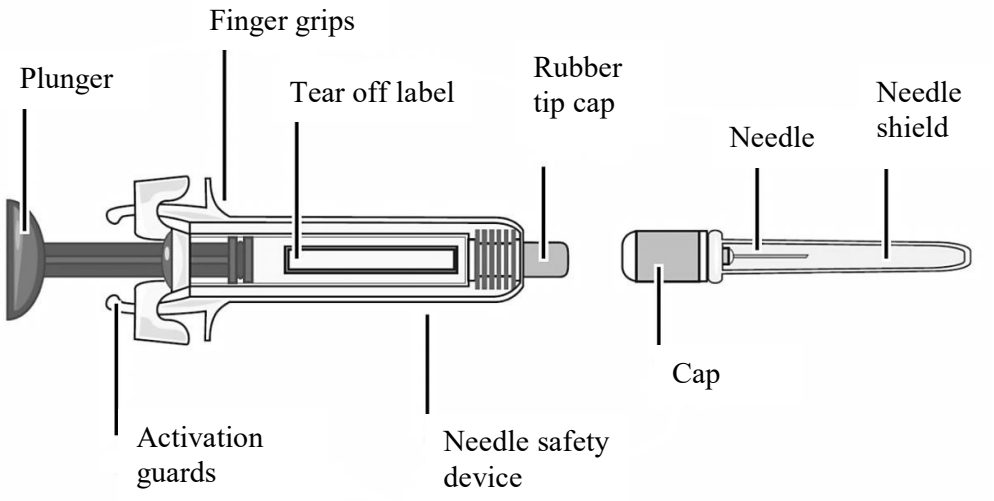
Store the syringe in its original box until ready to use.

Always store the syringe in a refrigerator at a temperature of 2 - 8°C.
Do not allow the medicine to freeze, and protect the medicine from light. Keep the syringe dry.

MATERIALS INCLUDED IN THE PACK (Figure A):

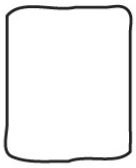
- A pre-filled syringe containing MIRCERA
- A separate injection needle

Figure A

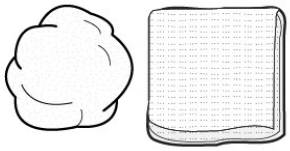


MATERIALS NOT INCLUDED IN THE PACK (Figure B):

Cleansing alcohol swabs



Sterile cotton ball or gauze



Puncture-resistant container or sharps container for safe disposal of needle and used syringe

Figure B

Assemble all of the supplies you will need for an injection on a clean, well-lit flat surface such as a table.

HOW TO GIVE THE INJECTION

Step 1: Allow the syringe to adjust to room temperature

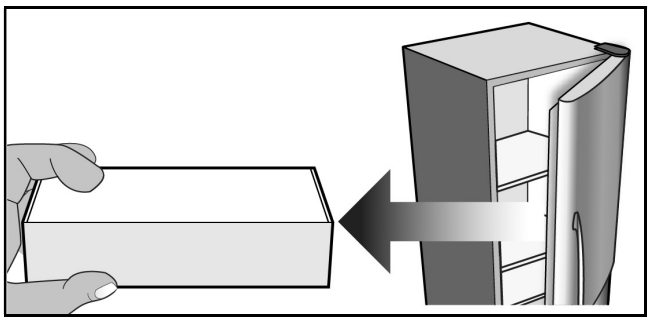


Figure C

Carefully remove the box containing the MIRCERA pre-filled syringe from the refrigerator. Keep the syringe in the box to protect it from light and allow it to reach room temperature for at least 30 minutes (Figure C).

- Not allowing the medicine to come to room temperature could result in an uncomfortable injection, and it may be difficult to depress the plunger.
- **Do not** warm up the syringe in any other way.

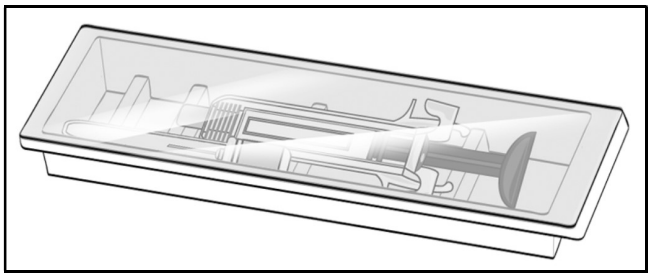


Figure D

Open the box and remove the plastic tray with the MIRCERA pre-filled syringe without peeling back the protective film (Figure D).

Step 2: Clean your hands

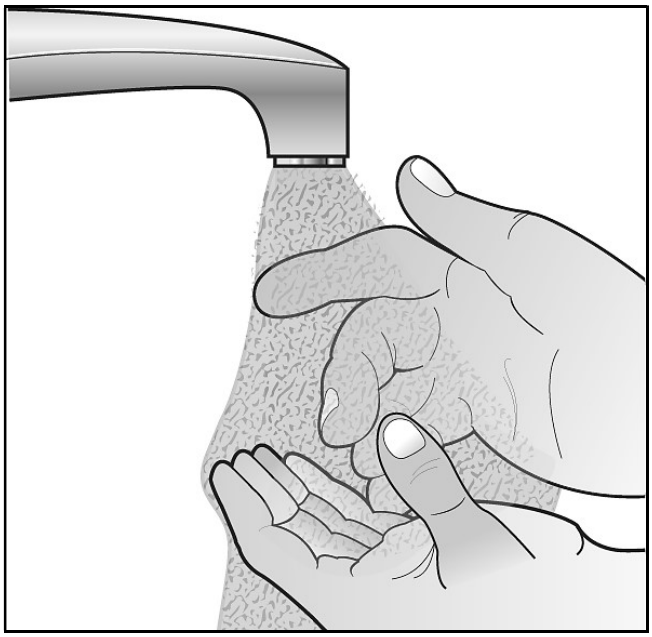


Figure E

Disinfect your hands well with soap and warm water or hands sanitizer (Figure E).

Step 3: Unpack and visually inspect the pre-filled syringe

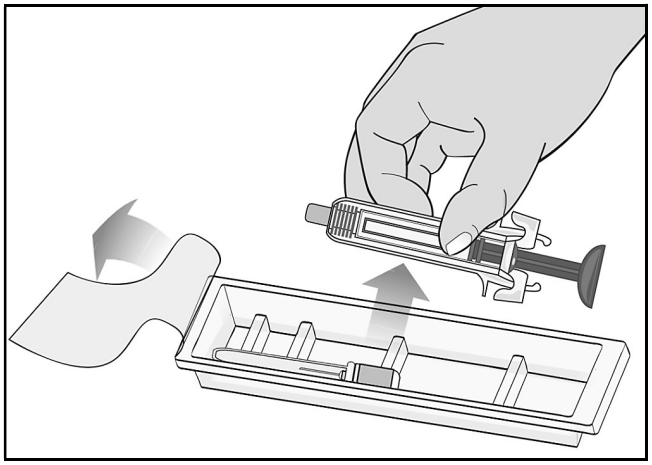


Figure F

Peel back the protective film from the plastic tray and remove the packed needle and the syringe, holding the syringe by the middle of the body without touching the activation guards (Figure F).

Only handle the syringe by the body, because any contact with the activation guards could cause premature release of the safety device.

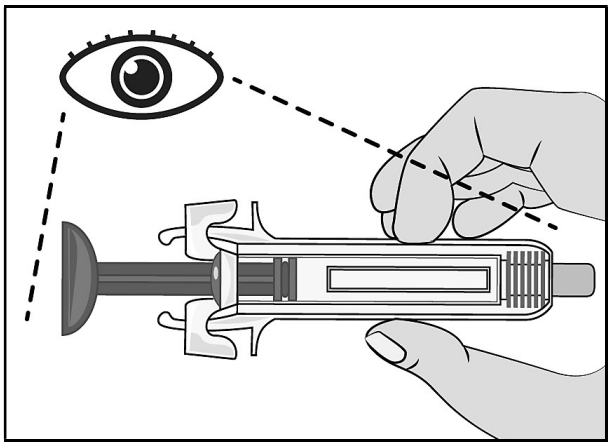


Figure G

Examine the syringe for damage and check the expiration date on the syringe and box. This is important to ensure that the syringe and medicine are safe to use (Figure G).

Do not use the syringe if:

- You have accidentally dropped the syringe.
- Any part of the syringe appears to be damaged.
- The contents are cloudy, hazy or contain particles.
- The expiration date has passed.

Step 4. Attach the needle to the syringe

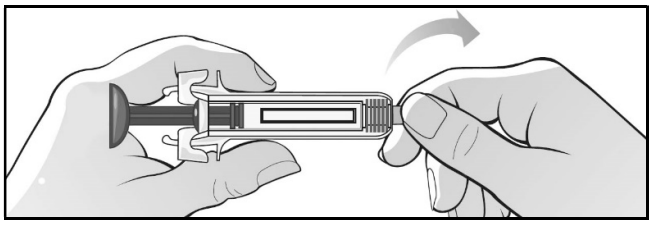


Figure H

Grasp the syringe in the middle of the body, hold the rubber tip cap firmly, and remove the rubber tip cap from the syringe (bend and pull) (Figure H).

- Once removed, immediately dispose of the rubber tip cap in the sharps/ puncture-resistant container.
- **Do not** touch the activation guards.
- **Do not** push the plunger.
- **Do not** pull on the plunger.

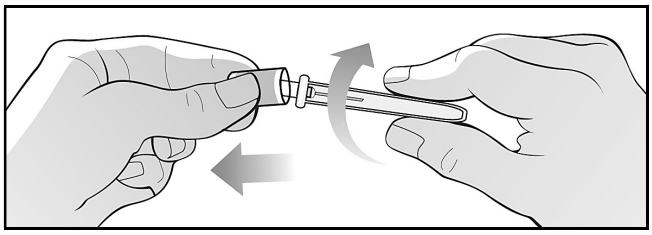


Figure I

Grasp the packaged needle firmly in both hands. Break the seal of the needle, using a twisting motion, and remove the needle cap (Figure I).
Immediately throw away the needle cap in the sharps / puncture-resistant container or sharps container.

Do not remove the needle shield that protects the needle.

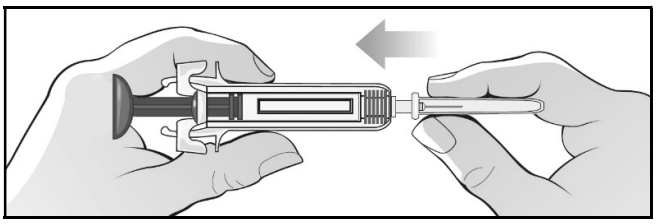


Figure J

Attach the needle to the syringe by pushing it firmly straight onto the syringe and by twisting or turning it slightly (Figure J).

Step 5. Remove the needle shield and prepare for injection

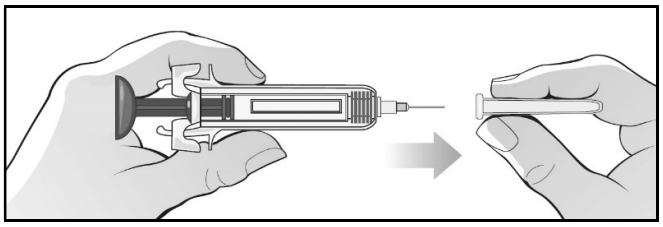


Figure K

Hold the syringe firmly with one hand in the middle of the body and pull the needle shield straight off with the other hand. Throw away the needle shield in the sharps/ puncture-resistant container or sharps container (Figure K).

- Once the needle shield is removed **do not** touch the needle or let it touch any surface, as the needle may become contaminated and may cause injury and pain if touched.
- You may see a drop of liquid at the end of the needle. This is normal.
- Never reattach the needle shield after removal.

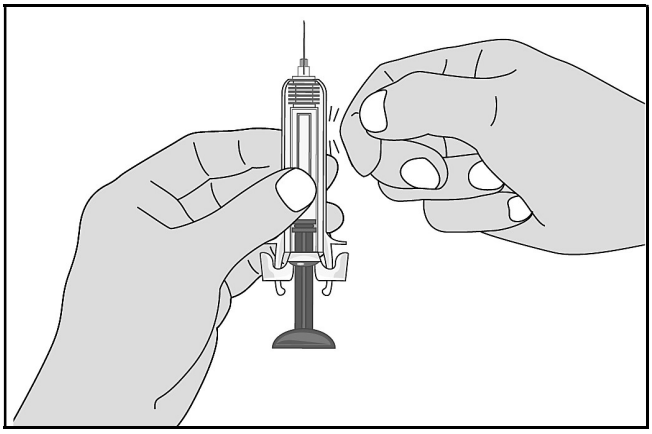


Figure L

To remove air bubbles from the pre-filled syringe, hold the syringe with the needle pointing up.
Tap the syringe gently to bring any bubbles to the top (Figure L and M).

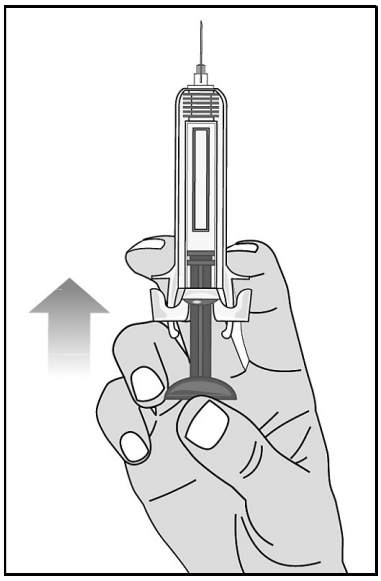


Figure M

Push the plunger up slowly to remove all air, as shown to you by a healthcare professional. (Figure M).

Step 6. Perform the injection

There are two different ways (routes) to inject MIRCERA into your body. Follow the recommendations of your healthcare professional about how you should inject MIRCERA.

SUBCUTANEOUS ROUTE:

If you are advised to inject MIRCERA under your skin, please administer your dose as described below.

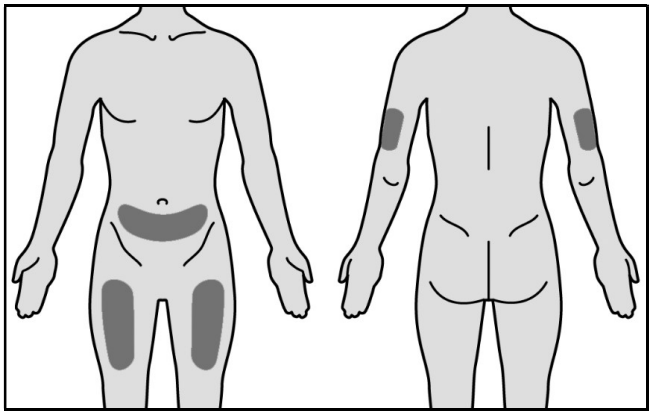


Figure N

Choose one of the recommended injection sites as shown.
You may inject MIRCERA into the upper arm, thigh or abdomen, but not in the area around the navel (belly button) (Figure N).
The back of the upper arm is not a recommended site for self-injection. Use this injection site only if you inject someone else.
When selecting an injection site:

- You should use a different injection site each time you administer an injection, at least three centimeters from the area you used for the previous injection.
- **Do not** inject into areas that could be irritated by a belt or waistband.
- **Do not** inject into moles,

scars, bruises, or areas where the skin is tender, red, hard or not intact.

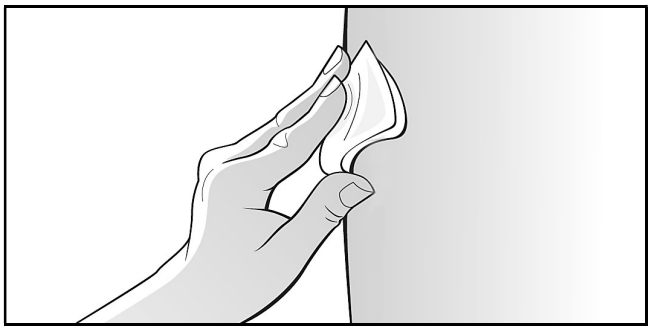


Figure O

Clean the chosen injection site area using an alcohol pad to reduce the risk of infection; carefully follow the instructions of the alcohol pad (Figure O).

- Let the skin dry for approximately 10 seconds.
- Be sure not to touch the cleaned area prior to the injection and **do not** fan or blow on the clean area.

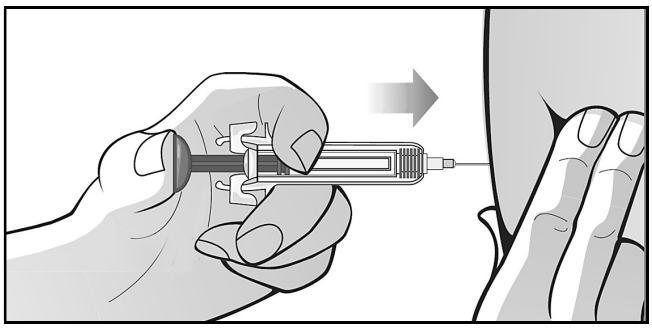


Figure P

Adopt a comfortable posture before performing an injection of MIRCERA.

To be sure the needle can be inserted correctly under the skin, use your free hand to pinch a fold of loose skin at the clean injection site. Pinching the skin is important to ensure that you inject under the skin (into fatty tissue) but not any deeper (into muscle). Injection into muscle could result in an uncomfortable injection (Figure P).

Carefully fully insert the needle into the skin at an angle of 90° in a quick, “dart-like” motion. Then keep the syringe in position and let go of the pinch of skin.

Do not move the needle while it is inserted in the skin.

Once the needle is fully inserted into the skin, slowly push the plunger with your thumb while

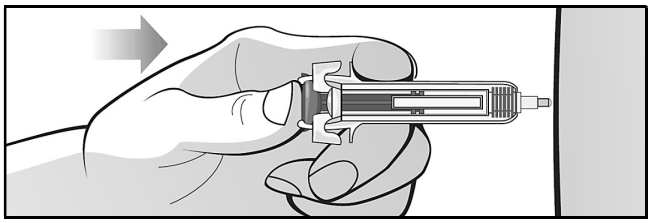


Figure Q

holding the syringe with the forefinger and the middle finger against the finger grips until all the medicine is injected. The plunger rod should be fully pushed down (depressed) and you should hear a click indicating the activation of the needle guard (Figure Q).

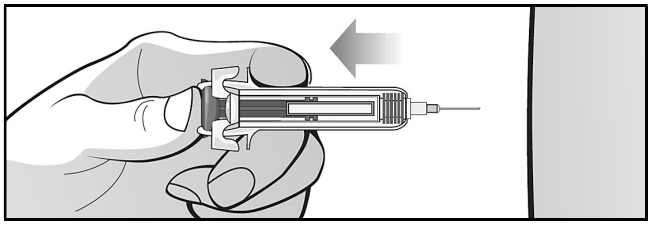


Figure R

Do not release the plunger before the end of injection or before the plunger is completely depressed.

Take the needle out of the skin **WITHOUT** releasing the plunger (Figure R).

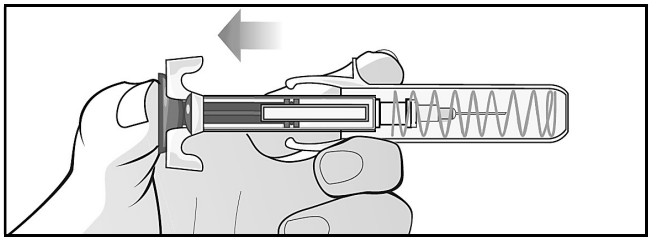


Figure S

Release the plunger, allowing the needle guard to protect the needle (Figure S).

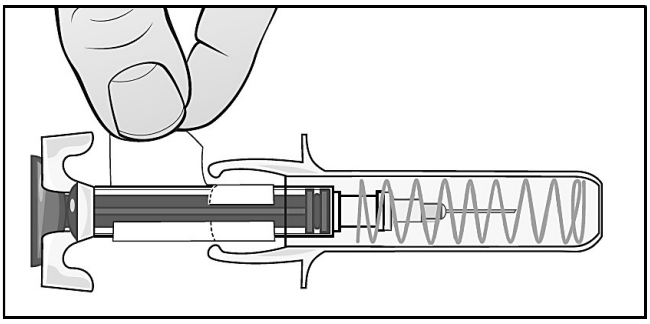


Figure T

Now, the tear-off label can be removed, if necessary (Figure T).

After the injection:

- Place a sterile cotton ball or gauze over the injection site and press for several seconds.
- **Do not** rub the injection site with a dirty hand or cloth.
- If needed, you may cover the injection site with a small bandage.

Dispose of the syringe:

- Throw away used syringes in a sharps/ puncture-resistant container.
- **Do not** try to replace the needle shield on the needle.
- **Do not** throw away used syringes or the sharps/ puncture-resistant container in household trash and **do not** recycle them.
- Dispose of the full sharps/ puncture resistant container.

INTRAVENOUS ROUTE:

If your healthcare professional has recommended injection of MIRCERA into a vein, you should follow the procedure described below.

After preparation of the syringe as described in steps 1 to 5:

Clean the venous port of the hemodialysis tubing with an alcohol swab as instructed by the provider or manufacturer.

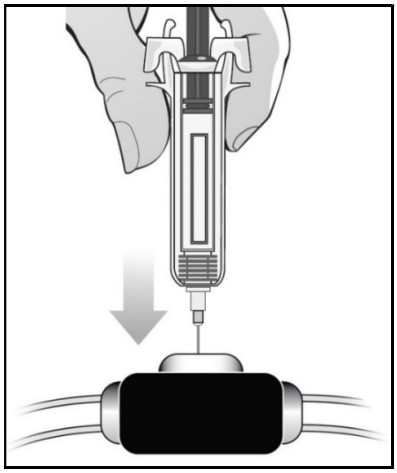


Figure U

Insert the needle of the pre-filled syringe into the **cleaned** venous port (Figure U).

Do not touch the injection site of the venous port.

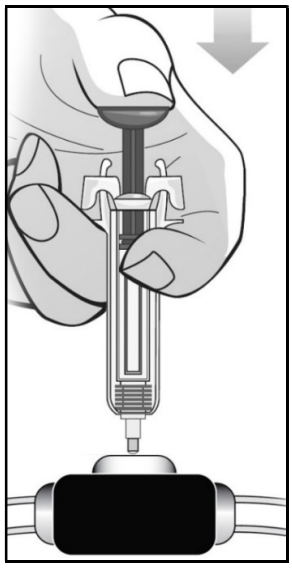


Figure V

Push the plunger with the thumb while holding the syringe with the forefinger and the middle finger against the finger grips until all the medicine is injected (Figure V).

Remove the pre-filled syringe from the venous port **WITHOUT** releasing the plunger.

Once removed release the plunger, allowing the needle guard to protect the needle.

Now, the tear-off label can be removed, if necessary (See Figure T).

Step 7: Dispose of the syringe

- Throw away used syringes in a sharps/ puncture-resistant container.
- **Do not** try to replace the needle shield on the needle.
- **Do not** throw away used syringes or the sharps/ puncture-resistant container in household trash and **do not** recycle them.
- Dispose of the full sharps/ puncture resistant container.