Mircera_PL_Ver 3.0

This leaflet was checked and approved by the Ministry of Health in October 2016 and was updated according to the guidelines of the Ministry of Health in March 2018

PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986

The medicine is dispensed with a doctor's prescription only

MIRCERA®

50 mcg/0.3 ml
75 mcg/0.3 ml
100 mcg/0.3 ml
150 mcg/0.3 ml
200 mcg/0.3 ml
360 mcg/0.6 ml

Pre-filled syringe

Composition:
Each pre-filled syringe contains:
Methoxy polyethylene glycol-epoetin beta

*For information about inactive ingredients, see section 6 - "Further Information".

Read this leaflet carefully in its entirety before using the medicine.
This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or pharmacist.
This medicine has been prescribed for you. Do not pass it on to others. It may harm them even if it seems to you that their medical condition is similar.

IMPORTANT INFORMATION FOR YOUR REVIEW

- The medicine **MIRCERA** is intended for subcutaneous (under the skin) or intravenous injection and comes in a pre-filled syringe. If you are self-injecting the medicine, follow the instructions for self-injection detailed at the end of the leaflet.
- Store the medicine in a refrigerator at a temperature of 2ºC-8ºC. Do not freeze. Keep the syringe in its original package in order to protect from light.

1) WHAT IS THE MEDICINE INTENDED FOR?

MIRCERA is intended for the treatment of anaemia caused by chronic kidney disease, in adults aged 18 years or older, manifested by symptoms such as tiredness, weakness and shortness of breath. This means that you have too few red blood cells and your haemoglobin level is too low (your body's tissues might not receive enough oxygen).
The medicine is produced by gene technology and causes an increase in the number of red blood cells and the haemoglobin level in your blood, by a mechanism similar to that of the natural hormone secreted in the body called erythropoietin.

Therapeutic Group: preparations for treatment of anaemia.
A medicine from the ESAs (Erythropoiesis Stimulating Agents) group.

2) BEFORE USING THE MEDICINE

X Do not use the medicine if:

- You have a known sensitivity (allergy) to the active ingredient (Methoxy polyethylene glycol-epoetin beta) or to any of the other ingredients contained in the medicine (listed in section 6).
- You suffer from high blood pressure that is not controlled.

! Special warnings regarding use of the medicine

The safety and efficacy of **MIRCERA** treatment in other indications, including anaemia in patients with cancer, have not been assessed.

Before treatment with MIRCERA

- A condition called PRCA (Pure Red Cell Aplasia - terminated or reduced production of red blood cells) due to anti-erythropoietin antibodies was observed in some patients treated with medicines from the ESAs (Erythropoiesis Stimulating Agents) group, including **MIRCERA**. Do not use **MIRCERA** if the doctor suspects or confirms that you have anti-erythropoietin antibodies in your blood.
- If you have chronic hepatitis C and you take medicines such as interferon and ribavirin, you should consult with the attending doctor because, in rare cases, a combination therapy of ESAs with interferon and ribavirin has led to a loss of treatment efficacy and to development of a condition called PRCA (a severe form of anaemia). Medicines from the ESAs group are not approved for the treatment of anaemia associated with chronic hepatitis C.
- If you are a cancer patient suffering from chronic kidney disease and anaemia and being treated with an ESA, you should be aware that medicines from the ESAs group might have a negative impact on your condition. You should discuss options for treatment of anaemia with the attending doctor.
- If you are suffering from disorders associated with abnormal haemoglobin structure, are suffering, or have suffered in the past, from bleeding, seizures, or high blood platelet count - it is unknown if **MIRCERA** has a different impact in these conditions. If you suffer from any of these conditions, the doctor will discuss it with you and will treat you with caution.
- **MIRCERA** is not appropriate for use in healthy people since use may lead to haemoglobin levels that are too high, thus causing heart and vascular system complications which may be life-threatening.

During treatment with MIRCERA

- If you are suffering from chronic kidney failure, especially if you do not adequately respond to **MIRCERA**, the attending doctor will check the dosage of the medicine. If you do not respond to treatment, repeated increases in the **MIRCERA** dosage may raise the risk of a heart or vascular problem and risk for heart attack, stroke and death.
- The attending doctor may initiate treatment with **MIRCERA** if your haemoglobin level is 10 g/dl or less. After initiation of treatment, the doctor will make sure to maintain your haemoglobin level between 10 and 12 g/dl.
- Your attending doctor will check the level of iron in your blood before and during **MIRCERA** treatment. If the level of iron is too low, the doctor may prescribe you an iron supplement.
- The attending doctor will check your blood pressure before and during **MIRCERA** treatment. If your blood pressure is high and cannot be controlled, either by appropriate medicines or a special diet, your doctor will discontinue treatment with **MIRCERA** or will reduce the dosage.
- Your attending doctor will check that your haemoglobin does not exceed a certain level, as high haemoglobin can put you at risk for heart or vascular systems complications and can increase risk of thrombosis (creation of a blood clot in an artery or a vein that may cause their blockage), including pulmonary embolism, heart attack, stroke and death.
- If during treatment with **MIRCERA** you feel tired, weak or suffer from shortness of breath, contact the attending doctor as this could mean that treatment with **MIRCERA** is not effective. The attending doctor will check that you do not have other causes of anaemia and may perform blood tests or examine the bone marrow.
  If you have developed PRCA, the attending doctor will discontinue treatment with **MIRCERA**, you will not receive another ESA and the doctor will treat your condition.

Children and adolescents
This medicine is not intended for use in children and adolescents, because it has not been studied in these populations.

MIRCERA and other medicines
Take special care with other medicines that stimulate red blood cell production: **MIRCERA** belongs to a group of medicines that stimulate red blood cell production like the human protein erythropoietin does. Your attending doctor will always record precisely the name of the medicine that you are using.

Serious skin reactions which include Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in association with epoetin treatment.
These severe skin reactions (TEN/SJS) may first appear as reddish lesions (target-shaped lesions) or as round spots, often with central blisters, on the body.
In addition, ulcers may occur in the mouth, throat, nose, genitals, and eyes (swollen and red eyes).
Occasionally, these serious skin rashes were preceded by fever and/or flu-like symptoms. The rash can develop into extensive skin peeling and life-threatening complications.
If you develop a severe rash or one of these skin symptoms, stop taking **MIRCERA** and contact your attending doctor or seek medical attention immediately.

If you are taking, or if you have recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist. Especially inform the doctor or pharmacist if you are taking interferon and ribavirin (see also section 2, sub-section Special warnings regarding use of the medicine).
Studies regarding interaction with other medicines have not been performed. There is no evidence that **MIRCERA** interacts with other medicines.

Use of the medicine and food
Food and drink do not affect **MIRCERA** treatment.

Pregnancy, breastfeeding and fertility
If you are pregnant or breastfeeding, consult the doctor or pharmacist before using any medicine.
MIRCERA has not been studied in pregnant or breastfeeding women.
Tell your doctor if you are pregnant, think you are pregnant or are planning to become pregnant. The attending doctor will determine which treatment is best for you during pregnancy.
Tell your doctor if you are breastfeeding or are planning to breastfeed. The attending doctor will advise you if you should stop or continue breastfeeding and whether to stop or continue treatment with **MIRCERA**.
MIRCERA has not shown evidence of impairing fertility in animals. The potential risk for humans is unknown.

Driving and using machines
Use of this medicine does not impair the ability to drive and operate machinery.

Important information about some of the ingredients in this medicine
This medicine contains less than 23 mg sodium per ml, i.e., this medicine is essentially 'sodium-free'.

3) HOW SHOULD YOU USE THE MEDICINE?

Always use according to the doctor's instructions.
Check with the doctor or pharmacist if you are not sure.
The attending doctor will use the lowest effective dosage to overcome the anaemia symptoms.
If you do not adequately respond to **MIRCERA**, the attending doctor will check your dosage and will inform you if the dosage of the medicine needs to be changed.
Initiation of treatment will be performed under the supervision of a healthcare professional. Later, the treatment will be administered by a healthcare professional or, after appropriate training, by self-injection (see instructions for self-injection at the end of this leaflet).
MIRCERA can be injected under the skin in the abdomen, arm or thigh, or intravenously. Your attending doctor will decide which option is best for you.
Your doctor will carry out blood tests regularly to monitor your response to treatment, by measuring your blood haemoglobin level.

Recommended dosage
The dosage and treatment regimen will be determined as per the doctor's instructions only. Do not exceed the recommended dose.
Your doctor may increase or decrease the dosage or temporarily stop the treatment in order to make adjustments per your haemoglobin level. Dosage adjustments will be done once a month, at most.

If you accidentally take a higher dosage, contact the attending doctor or pharmacist, since it may be necessary to perform blood tests and discontinue the treatment.
If you took an overdose, or if a child has accidentally swallowed the medicine, refer immediately to a doctor or proceed to a hospital emergency room and bring the package of the medicine with you.

If you forget to take this medicine at the required time, take the next dose as soon as you remember and contact the attending doctor regarding the schedule of the following doses.

If you stop taking the medicine
Treatment with **MIRCERA** is normally long-term. It can, however, be stopped at any time, on the advice of the attending doctor.
Adhere to the treatment regimen as recommended by the doctor.
Even if there is an improvement in your health, do not stop treatment with the medicine without consulting the doctor.
Do not take medicines in the dark! Check the label and dose each time you take medicine. Wear glasses if you need them.
If you have further questions regarding use of this medicine, consult the doctor or pharmacist.

4) SIDE EFFECTS

As with any medicine, use of **MIRCERA** may cause side effects in some users. Do not be alarmed by the list of side effects. You may not suffer from any of them.

Refer to the doctor immediately if the following rare side effects occur *(effects that occur in 1-10 users in 10,000):*

- Very high blood pressure that causes a headache, especially a sudden, stabbing, migraine-like headache, confusion, speech disturbances or convulsions (hypertensive encephalopathy).
  If you have these symptoms, contact the doctor immediately to receive treatment.
- Hypersensitivity (allergic reaction that may cause wheezing or difficulty in breathing; swollen tongue, face, or throat or swelling around the injection site; a dizzy feeling, fainting or collapse). If you have these symptoms, contact the doctor immediately to receive treatment.

Additional side effects
Common side effects (effects which occur in 1-10 users in 100):

- high blood pressure

Uncommon side effects (effects that occur in 1-10 users in 1,000):

- headache
- blood clots in the dialysis access line

Rare side effects (effects which occur in 1-10 users in 10,000):

- red skin rash that may be accompanied by pimples or spots on the skin
- hot flashes

During clinical studies, a slight decrease in the platelet blood count was observed. There were spontaneous reports of platelet counts lower than the normal range (thrombocytopenia).

Hypersensitivity reactions, including cases of anaphylactic reaction and severe skin rashes, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in association with epoetin treatment.
They can appear as reddish lesions (target-like lesions) or as round spots, often with central blisters, on the body. In addition, there may be skin peeling, ulcers in the mouth, throat, nose, genitals, and eyes that may have been preceded by fever and flu-like symptoms.

If you develop these symptoms, stop taking **MIRCERA** and contact your attending doctor or seek medical attention immediately (see section 2).

As with other medicines from the ESAs group, cases of thrombosis (formation of a blood clot in an artery or a vein which may cause their blockage), including pulmonary embolism, have been reported at an unknown frequency.

A side effect of PRCA (Pure Red Cell Aplasia, i.e., terminated or reduced production of red blood cells) has been observed in patients treated with ESAs, including **MIRCERA**, due to anti-erythropoietin antibodies.

If one of the side effects worsens or if you suffer from a side effect not mentioned in the leaflet, consult with the doctor.

Side effects can be reported to the Ministry of Health by clicking on the "Reporting side effects following drug treatment" link found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or through the following link: https://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

5) HOW SHOULD THE MEDICINE BE STORED?

- Avoid poisoning! This medicine, and any other medicine, should be kept in a safe place out of the reach of children and/or infants in order to avoid poisoning.
- Keep the syringe and the container designated for disposal of the used needle and syringe out of the reach of children and/or infants.
- Do not induce vomiting unless explicitly instructed to do so by the doctor.
- Do not use the medicine after the expiry date (exp. date) appearing on the package and the syringe. The expiry date refers to the last day of that month.
- Storage conditions: Store in a refrigerator: 2ºC-8ºC (this temperature range prevails in most household refrigerators). Do not freeze. Keep the syringe in the original carton package in order to protect from light, until you are ready to inject the medicine.

For the patient's information: You may remove your **MIRCERA** syringe from the refrigerator and store it at a room temperature up to 30ºC, and use it within one month from the day it was removed from the refrigerator. During the period that the **MIRCERA** syringe has been stored outside of the refrigerator, at a room temperature that does not exceed 30ºC, do not return the syringe to the refrigerator before using.
Use within one month since removing it from the refrigerator.
Only solutions which are clear, colourless to yellowish and free of visible particles should be injected.
Do not discard the medicine into the household waste or wastewater. Ask the pharmacist how to throw away medicines you no longer need. These measures will help protect the environment.

6) FURTHER INFORMATION

In addition to the active ingredient, the medicine also contains:
Water for injection, Mannitol, Sodium sulphate anhydrous, L-methionine, Sodium dihydrogen phosphate monohydrate, Poloxamer 188, diluted Hydrochloric acid, Sodium hydroxide diluted solution.

What does the medicine look like and what are the contents of the package?
The active ingredient in **MIRCERA** is methoxy polyethylene glycol-epoetin beta.

Each package of the preparation contains one pre-filled syringe that consists of: 50, 75, 100, 150 or 200 mcg/0.3 ml and 360 mcg/0.6 ml.
** Not all dosages of the preparation may be marketed.
MIRCERA is a solution for injection that comes in a pre-filled syringe. The solution is clear, transparent to slightly yellow in color and free of visible particles.

Manufacturer:
Roche Diagnostics GmbH, Germany - Sandhofer strasse 116, Mannheim, Germany

This leaflet was checked and approved by the Ministry of Health in October 2016 and was updated according to the guidelines of the Ministry of Health in March 2018

License holder: Roche Pharmaceuticals (Israel) Ltd., P.O.B. 6391, Hod Hasharon 4524079.

Registration number of the medicine in the National Drug Registry of the Ministry of Health:
MIRCERA 50 mcg/0.3 ml pre-filled syringe: 138.53.31749.00.
MIRCERA 75 mcg/0.3 ml pre-filled syringe: 138.54.31750.00.
MIRCERA 100 mcg/0.3 ml pre-filled syringe: 138.55.31751.00.
MIRCERA 150 mcg/0.3 ml pre-filled syringe: 138.56.31752.00.
MIRCERA 200 mcg/0.3 ml pre-filled syringe: 138.57.31753.00.
MIRCERA 360 mcg/0.6 ml pre-filled syringe: 140.01.31905.00.

Roche

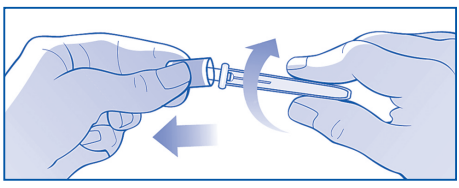
INSTRUCTIONS FOR SELF-INJECTING MIRCERA PRE-FILLED SYRINGE:

- It is important to read and follow the instructions below carefully so that you will be able to use the pre-filled syringe correctly and safely. Do not attempt to inject the medicine alone until you are sure that you understand how to inject the medicine.
- **Use MIRCERA exactly as the doctor has instructed you. If you are unsure about the injection technique, consult your doctor or nurse.**
- **MIRCERA** pre-filled syringe is ready for use. The medicine can be self-injected under the skin or in patients on dialysis - through the dialysis access line, according to the attending doctor's instructions. The following injecting instructions refer to self-injection under the skin.

Important information:
- Use **MIRCERA** syringe only if you received a prescription for the medicine.
- Make sure that the package you received contains the dosage prescribed for you by the attending doctor.
- Do not use the syringe if the plastic tray containing the syringe or the syringe has been damaged.
- Use the syringe only if the solution is clear, free of visible particles and colourless or slightly yellow.
- Do not attempt to take the syringe apart.
- Do not hold or pull the syringe plunger.
- Do not remove the needle shield until you are ready to perform the injection.
- Do not swallow the liquid in the syringe and do not inject through clothing.
- Do not use the syringe more than once.
- Do not touch the side release clips in order not to damage the syringe and make it unusable.
- Make sure that the syringe is dry.

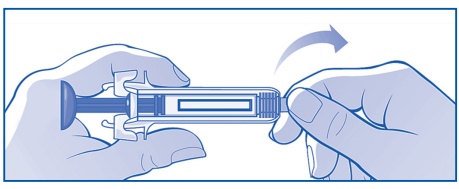
The MIRCERA package contains:
1. One pre-filled syringe + an injection needle (27G1/2) wrapped in a transparent plastic tray.
2. Each pre-filled syringe contains 0.3 ml or 0.6 ml (depending on the dosage) of clear, colourless to yellowish solution.

Before the injection:
1. Make sure that you have: an alcohol swab, sterile gauze and a special container for disposing the used needle and syringe.
2. Prepare the items necessary for injection on a clean, well-lit and flat surface, such as a table.
3. Take the **MIRCERA** package out of the refrigerator. Keep the syringe in its original carton package to protect it from light and to allow it to reach room temperature, up to 30°C. This should happen within 30 minutes of removing the medicine from the refrigerator.
4. If the medicine is not injected at room temperature, the injection may be uncomfortable and it may be difficult to push the plunger. Do not heat the syringe in any other way.
5. Remove the transparent tray from its original carton package without opening the tray wrapper.
6. Wash your hands thoroughly with hot water and soap or with a disinfectant.
7. Open the tray wrapper and remove the syringe and needle from the transparent tray by holding the body of the syringe, without touching the side release clips, which may lead to release of the protective device.
8. Look at the syringe and check the expiry date (exp. date) on the syringe and on the carton package, to make sure that the syringe is safe for use. Do not use the syringe if it fell, if any part of it looks damaged, if the solution in the syringe is cloudy or contains particles or if the expiry date has passed.

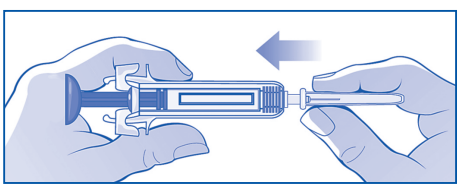


Preparing the syringe and needle for injection:

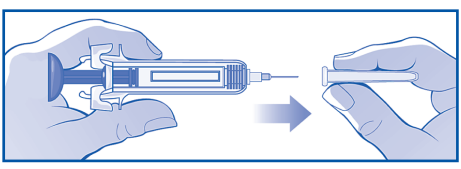
1. Hold the needle well with both hands. Break the seal of the needle, using a twisting motion, and remove the plastic cap.
   Immediately discard the needle cover in a closed and safe container.
   At this stage, do not remove the needle shield protecting the front part of the needle.



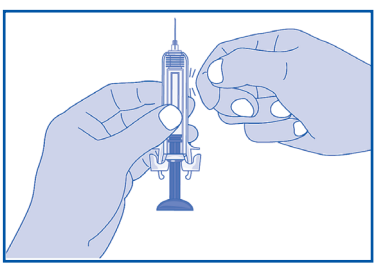
2. Remove the rubber cap from the syringe tip, by bending and pulling it.
3. Do not touch the release clips of the protective device.
4. Do not pull or push the plunger.



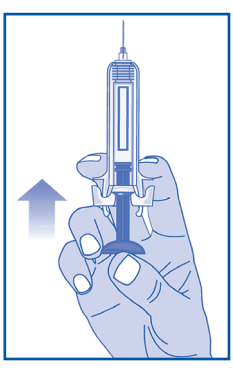
5. Attach the needle to the syringe by pushing firmly.



6. Hold the syringe in one hand and remove the plastic needle shield with the other hand.
7. Discard the needle shield in a closed and safe container.
8. Be careful not to touch the needle and not to let the needle touch any surface, as the needle may become contaminated and may cause injury and pain.
9. You may see a drop of fluid at the tip of the needle; this is OK.
10. Do not reattach the needle shield after removing it.



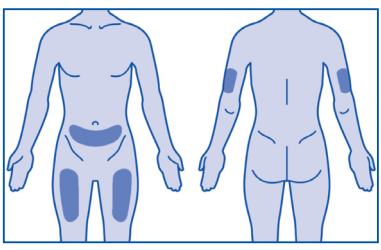
11. To remove air bubbles from the syringe, hold the syringe with the needle pointing up. Tap the syringe gently to bring the air bubbles to the top.



12. Push the plunger up slowly to remove the air, as shown to you by a healthcare professional.

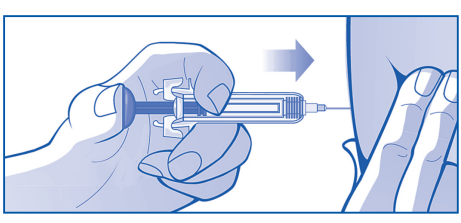
Injecting the solution:
If your attending doctor has advised you to inject the medicine through the dialysis line or intravenously, please receive the treatment as recommended to you.

If your attending doctor recommended that you receive the medicine as an **injection under the skin**, please read the following instructions for injection.

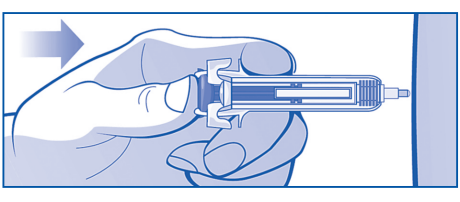


1. Choose the injection site, in the thigh, arm or abdomen (except around the navel and waistline). Do not choose the same injection site you chose last time. The new injection site should be at a distance of at least 3 cm from the last injection site.
2. Do not inject **MIRCERA** in areas that may be irritated by a belt. Do not inject into moles, scars, bruises, or into an area where the skin is tender, red, hard or damaged.

3. Cleanse and disinfect the skin at the designated injection site with an alcohol swab in order to reduce the chance of infections.
4. Wait until the area is dry (approximately 10 seconds).
5. Do not touch the area again before the injection, and do not blow or fan the area.



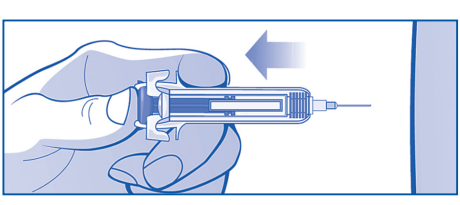
6. With one hand, create a fold of skin (at the clean injection area) by pinching lightly between the thumb and forefinger. This step is important to ensure injection under the skin (into the fat tissue), but no deeper (to the muscle layer). Injection into the muscle may cause discomfort.
7. With the other hand holding the syringe quickly insert the entire needle into the skin fold.



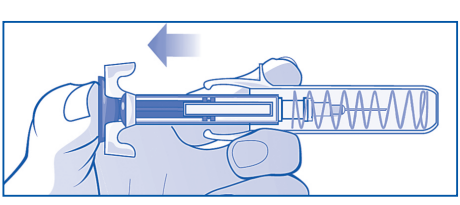
8. Using the thumb, slowly push the plunger while holding the syringe between your fingers until the entire recommended dose is injected.

   Do not move the needle when it is inserted into the skin.

   Do not release the plunger until completion of the injection or before the plunger is fully depressed.



9. Continue pressing on the syringe plunger and remove the needle from the skin.



10. Release the plunger. Upon releasing the plunger, the safety mechanism will be activated and the needle will automatically be drawn into the syringe.

11. Press on the injection site with a sterile gauze or cotton ball for several seconds.
12. Do not massage the injection site with the hands or a dirty cloth.
13. In case of bleeding, the area may be covered with an adhesive bandage.

Disposal of the syringe:
The syringe is intended for single use and must be discarded after the injection. Dispose of the syringe in a closed and safe container. Do not try to replace the plastic needle shield. Do not dispose of the container or used syringes via household waste and do not recycle them. Consult with the doctor/pharmacist/nurse about how to dispose of the container.