Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) -1986

This medicine is dispensed with a doctor's prescription only

Kovaltry® 250 IU
Kovaltry® 500 IU
Kovaltry® 1000 IU
Kovaltry® 2000 IU

Powder and solvent for solution for injection

Each vial of powder contains:
Nominally 250, 500, 1000, or 2000 IU (International Units) recombinant human coagulation factor VIII (octocog alfa).

After reconstitution with water for injection:
1 mL of Kovaltry 250 IU contains approximately 100 IU (250 IU/2.5 mL) of recombinant human coagulation factor VIII (octocog alfa),
1 mL of Kovaltry 500 IU contains approximately 200 IU (500 IU/2.5 mL) of recombinant human coagulation factor VIII (octocog alfa),
1 mL of Kovaltry 1000 IU contains approximately 400 IU (1000 IU/2.5 mL) of recombinant human coagulation factor VIII (octocog alfa),
1 mL of Kovaltry 2000 IU contains approximately 400 IU (2000 IU/5 mL) of recombinant human coagulation factor VIII (octocog alfa).

Inactive ingredients and allergens: See section 2 under "Important information about some of this medicine's ingredients" and section 6 "Additional Information".

Read the entire leaflet carefully before you start using this medicine.
This leaflet contains concise information about this medicine. If you have any further questions, consult your doctor or pharmacist.

This medicine has been prescribed for the treatment of your illness. Do not pass it on to others. It may harm them even if it seems to you that their illness is similar to yours.

1) What is this medicine intended for?

Kovaltry is used for treatment and prevention of bleeding in adults, adolescents and children of all ages with haemophilia A (congenital factor VIII deficiency).

Therapeutic Group: Kovaltry belongs to a group of medicines for prevention of bleeding that contains the coagulation factor number VIII. The medicine contains the active substance human recombinant coagulation factor VIII, also called octocog alfa. Kovaltry is prepared by recombinant technology without addition of any human- or animal-derived ingredients in the manufacturing process. Factor number VIII is a protein found naturally in the blood and helps it to clot.

2) Before using this medicine

Do not use this medicine if:

- You are sensitive (allergic) to the active substance octocog alfa or to any of the other ingredients contained in this medicine. For the list of the excipients, see section 6 "Additional information".
- You are sensitive (allergic) to mouse or hamster-derived proteins.

Do not use Kovaltry if either of the above applies to you. If you are not sure, talk to your doctor before using this medicine.

Special warnings about using this medicine
Special caution is required with the use of Kovaltry. **Before treatment with Kovaltry, tell your doctor if:**

- You experience tightness in the chest, dizziness (including when changing from sitting or lying down to standing up), hives (urticaria), wheezing while breathing, nausea or fainting. These may be signs of a rare severe sudden allergic reaction (an anaphylactic reaction) to Kovaltry.
  If this occurs, **stop the treatment immediately** and seek medical help.
- Bleeding is not being controlled with the usual dosage of Kovaltry you are taking. The formation of inhibitors (antibodies) is a known complication that can occur during treatment with all Factor VIII medicines. These inhibitors, especially at high levels and depending on the severity of the disease, stop the treatment from working properly. This risk is higher during the first 50 days of exposure. Patients taking Kovaltry need to be monitored carefully for the development of these inhibitors. If your or your child's bleeding is not being controlled with Kovaltry, tell your doctor immediately.
- You have previously developed factor VIII inhibitors to a different preparation. You may be at risk of developing such an inhibitor again if switching between preparations that contain factor VIII.
- You have a confirmed heart disease or are at risk of heart disease.
- For the administration of Kovaltry to you there is a need for access to a central vein using a special device. The use of such a device may be associated with complications including: local infections, bacterial infection of the blood (bacteraemia) and the formation of blood clots in the blood vessels (thrombosis) where the catheter is inserted.

Children and adolescents
The warnings listed in this leaflet apply to patients of all ages, adults and children.

Tests and follow-up
It is strongly recommended that laboratory tests be performed at suitable intervals during the course of treatment with this medicine to ensure that the dose have been given provides adequate levels of factor VIII and that these levels are maintained.
For major surgery in particular, close monitoring of the replacement therapy by means of coagulation analysis must be carried out.

Other medicines and Kovaltry
If you are taking, or have recently taken any other medicines, including nonprescription medications and dietary supplements, tell your doctor or pharmacist.

Pregnancy, breastfeeding, and fertility
There is no experience with using medicines that contain factor VIII during pregnancy or breastfeeding since haemophilia A rarely occurs in women.
If you are pregnant or breastfeeding, think you may be pregnant or are planning to get pregnant, consult with a doctor before using the medicine.
Kovaltry is unlikely to affect fertility in females or males as the active substance is naturally occurring in the body.

Driving and using machines
If you experience dizziness or any other symptoms affecting your ability to concentrate or react, do not drive and do not operate machines until this reaction subsides.
Children must be cautioned against riding a bicycle, playing near a road, and similar activities.

Important information about some of this medicine's ingredients
The medicine contains less than 1 mmol of sodium (23 mg) per dose, so it is considered essentially "sodium-free".

Documentation
It is recommended that every time that Kovaltry is used, the doctor will document the name of the preparation and batch number.

3) How to use this medicine?

Treatment with Kovaltry will be started by a doctor who is experienced in the care of patients with haemophilia A.

Always use this medicine according to the doctor's instructions. You should check with your doctor if you are not sure about the dose or about how you should use this medicine.

The number of coagulation factor VIII units is expressed in International Units (IU).

The dosage and the treatment regimen will be determined by the doctor only.

Do not exceed the recommended dose.

Duration of treatment
The doctor will tell you how often and at what intervals Kovaltry should be taken.
Usually, Kovaltry treatment is for life.

How Kovaltry is given
The medicine is intended for intravenous injection over 2-5 minutes depending on the total injection volume and your comfort level. The preparation is to be used within 3 hours from reconstitution. From a microbial point of view, the preparation is to be used immediately after reconstitution.

Preparing Kovaltry
Only the items (vial adapter, pre-filled syringe containing the solvent, infusion set) that are provided with each package of the preparation should be used. If any component of the package is opened or damaged, do not use it.

After reconstitution and before use, **the preparation must be filtered** to remove any possible particles in the solution. **The filtering is done by using the vial adapter.**

Do not use the infusion set that is in the package to draw blood because it contains a built-in filter.

This medicine **must not** be mixed with other solutions for infusion. Do not use a solution that contains particles or looks cloudy. Follow the directions carefully and **use the detailed instructions for reconstitution and use provided at the end of this leaflet.**

If you have accidentally taken a higher dosage, refer to the doctor
There have been no reported events of overdose with recombinant coagulation factor VIII.
If you took an overdose or a child swallowed the medicine by mistake, refer immediately to the doctor or to the emergency room of a hospital and take the medicine package with you.

If you forgot to take the medicine
- Immediately inject the next dose and continue injections at the usual intervals as recommended to you by your doctor.
- Do not inject a double dose to make up for a forgotten dose.

Adhere to the treatment as recommended by the doctor.

If you stop taking Kovaltry
Do not stop the treatment with the medicine without consulting the doctor.

Do not take medicines in the dark! Check the label and the dose every time you take medicine. Wear glasses if you need them.
If you have any further questions about using this medicine, consult your doctor.

4) Side effects

Like with all medicines, using Kovaltry may cause side effects in some users. Do not be alarmed by this list of side effects; you may not experience any of them.

The **most serious** side effect is an **allergic reaction** which may be anaphylactic shock (an uncommon, severe allergic reaction, affecting blood pressure and breathing). **If allergic or anaphylactic reactions occur, immediately stop the injection/infusion and immediately talk with your doctor.** Occurrence of any of the following symptoms during the injection/infusion **can** be an early warning sign for allergic or anaphylactic reactions:
- tightness in the chest/general feeling of being unwell
- dizziness
- feeling faint upon standing indicating a mild reduction in blood pressure
- nausea

For children not previously treated with Factor VIII medicines, **inhibitor** antibodies (see section 2) may form very commonly (more than 1 in 10 patients).
For patients who have received previous treatment with Factor VIII (more than 150 days of treatment) inhibitor antibodies (see section 2) may form uncommonly (less than 1 in 100 patients). If this happens **your medicine may stop working properly and you may experience persistent bleeding. If this happens, you should contact your doctor immediately.**

Additional side effects
Common side effects - effects that occur in up to 1 out of 10 users
- stomach pain or discomfort
- indigestion
- fever
- local reactions where you injected the medicine (e.g. bleeding under the skin, intense itching, swelling, burning sensation, temporary redness)
- headache
- dizziness
- trouble sleeping
- hives (urticaria)
- rash/itchy rash

Uncommon side effects - effects that occur in up to 1 out of 100 users
- enlarged lymph nodes (swelling under the skin of the neck, armpit or groin)
- palpitation (feeling your heart beating hard, rapidly, or irregularly)
- rapid heartbeat
- a strange taste in the mouth
- flushing (redness of the face)

If you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, consult your doctor.
You can report side effects to the Ministry of Health by following the link 'Reporting Side Effects of Drug Treatment' on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects. You can also use this link: https://sideeffects.health.gov.il

5) How to store the medicine?

- Prevent poisoning! To prevent poisoning, keep this, and all other medicines, in a closed place, out of the reach and sight of children and/ or infants. Do not induce vomiting unless explicitly instructed to do so by a doctor.
- **Do not use** the medicine after the expiry date (exp. date) which is stated on the package. The expiry date refers to the last day of that month.

Storage conditions
- Store in a refrigerator (2°C–8°C). This temperature range is usually prevalent in home refrigerators). Do not freeze. Keep the medicine in the original package in order to protect from light.
  The medicine may be stored at room temperature (up to 25°C) in the outer carton for a limited period of 12 months. If you store this medicine at room temperature, the medicine expiry date will be 12 months from the day it was taken out from the refrigerator or the expiry date indicated on the package, whichever comes first. The new expiry date must be noted on the outer carton.
- After the reconstitution, **do not** refrigerate the solution. The preparation is to be used within 3 hours from reconstitution. From a microbial point of view, the preparation is to be used immediately after reconstitution. This preparation is for single use only. Any remainders of the solution should be thrown away.
- **Do not** use the preparation if you notice particles or if the solution is cloudy.
- **Do not** dispose of medicines via wastewater or the household waste. Consult with a pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6) Additional Information

- **In addition to the active ingredient, the medicine also contains:**
  Glycine, sucrose, histidine, sodium chloride, calcium chloride dihydrate, polysorbate 80, acetic acid glacial (for pH adjustment).
  Solvent: Water for injections.
- **What the medicine looks like and the content of the package:**
  Kovaltry is provided as a pack that includes a powder and solvent for the preparation of a solution for injection. The powder is dry and white to yellow. The solution obtained after the reconstitution is clear.
  Each package of Kovaltry contains a vial with powder, a pre-filled syringe with solvent, a separate plunger. In addition, it includes a vial adapter and an infusion set (for injection into the vein).
  The components required for reconstitution and injection are provided with each package of the preparation.
- Name and address of the registration holder: Bayer Israel Ltd., 36 Hacharash St., Hod Hasharon 45240.
- Name and address of the manufacturer: Bayer AG, Leverkusen, Germany.
- Revised in October 2022 according to MOH guidelines
- Registration number of the medicine in the National Drug Registry of the Ministry of Health:
  Kovaltry 250 IU 158-43-34962-00
  Kovaltry 500 IU 158-44-34963-00
  Kovaltry 1000 IU 158-45-34964-00
  Kovaltry 2000 IU 158-46-34965-00

Detailed instructions for reconstitution and injection of Kovaltry using vial and vial adapter:

You will need alcohol swabs, gauze pads, plasters (adhesive bandage) and tourniquet. These items are not included in the Kovaltry package.

1. Wash your hands thoroughly using soap and lukewarm water.
2. Using your hands, warm the unopened vial and the syringe to a comfortable temperature (do not exceed 37°C).
3. Remove the cap from the vial **(A)**, wipe the rubber stopper with an alcohol swab and allow it to air dry before use.

4. Place the **vial** on a surface that is stable and not slippery. Peel off the paper cover from the plastic housing protecting the vial adapter. **Do not remove** the adapter from the plastic housing. Whilst holding the adapter via the plastic housing, place it over the vial containing the powder and firmly press it down to the vial opening **(B)**. At this point with each package of the preparation.

5. Hold the pre-filled syringe upright, grasp the plunger of the syringe as shown in the diagram and attach the plunger by firmly screwing it clockwise into the threaded stopper **(C)**.

6. Hold the body of the syringe, break the cap off the tip **(D)**. Do not touch the syringe tip with your hand and do not bring it into contact with any other surface. Set the syringe aside for later use.

7. Now remove and discard the adapter housing **(E)**.

8. Screw the pre-filled syringe to the adapter by turning it clockwise **(F)**.

9. Inject the solvent by slowly pushing down on the plunger of the syringe **(G)**.

10. Swirl the vial gently until all of the powder of the preparation has dissolved **(H)**. Do not shake the vial. Be sure that the powder has completely dissolved. Before using, visually inspect the solution for particles or discoloration. Do not use solutions containing visible particles or cloudy solutions.

11. Hold the vial so that its nozzle is facing downwards and it is above the adapter and the syringe **(I)**. Fill the syringe by drawing the syringe plunger out slowly and smoothly. Make sure that the entire content of the vial is drawn into the syringe. Hold the syringe upright and push the plunger until no air is left in the syringe.

12. Apply a tourniquet to the arm.
13. Determine the point of injection and clean the skin with an alcohol swab.
14. Puncture the vein and secure the infusion set with a plaster.
15. Whilst holding the adapter in place, remove the syringe from the vial adapter (the adapter should remain attached to the vial). Attach the syringe to the infusion set, ensure that no blood enters the syringe **(J)**.

16. Remove the tourniquet.
17. Inject the solution into the vein over 2-5 minutes, while observing the position of the needle. The speed of injection should be adapted to the patient's comfort, but should not be faster than 2 mL per minute.
18. If a further dose needs to be injected, use a new syringe with powder reconstituted as described above.
19. If the injection of a further dose is not required, remove the infusion set and syringe. Hold a pad firmly over the injection site while the patient's hand is outstretched for about 2 minutes. Finally, apply gentle pressure to the injection site and consider using a plaster if necessary.
20. It is recommended that every time you use Kovaltry, you note down the name and the batch number of the preparation.
21. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

DOR-Kov-PIL-0123-14