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

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

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

Inactive and allergenic ingredients: see section 6 "Further Information" and section 2 "Important information about some of the ingredients of the medicine".

Read the 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 to treat your ailment. Do not pass it on to others. It may harm them, even if it seems to you that their ailment is similar.

1) WHAT IS THE MEDICINE INTENDED FOR?

Kovaltry is intended for the treatment and prevention of bleeding in adults, adolescents and children of all ages with type A hemophilia (a congenital factor VIII deficiency).

Therapeutic group: Kovaltry belongs to the group of coagulation factor VIII-containing medicines for the prevention of bleeding. 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 components in the manufacturing process. Factor VIII is a protein naturally found in the blood that helps to clot it.

2) BEFORE USING THE MEDICINE

Do not use the medicine if:
- You are sensitive (allergic) to the active ingredient octocog alfa or to any of the additional ingredients contained in the medicine. For the list of inactive ingredients, see section 6 "Further Information".
- You are sensitive (allergic) to mouse or hamster proteins.

Do not use Kovaltry if any of the aforementioned conditions apply to you. If you are uncertain, consult your doctor before using the medicine.

Special warnings regarding use of the medicine

Special caution is required when using Kovaltry and you should consult a doctor or pharmacist if:
- You experience tightness in the chest, dizziness (including when getting up from sitting or lying to a standing position), hives, urticaria, wheezing, nausea or faintness. These may be signs of a severe sudden allergic reaction (anaphylactic reaction) to Kovaltry. If this happens, **stop treatment immediately** and seek medical help.
- Your bleeding is not being controlled with your usual dosage of Kovaltry. The formation of inhibitors (antibodies) is a known complication that can occur during treatment with all factor VIII preparations. These inhibitors, especially at high levels, and depending on the severity of the disease, prevent the treatment from working properly. This risk is higher in the first 50 days of exposure.
  Patients taking Kovaltry should 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 previously developed factor VIII inhibitors to a different preparation. If you switch between factor VIII-containing preparations, you may be at risk of developing such an inhibitor again.
- You are suffering from a confirmed heart disease or are at risk of heart disease.
- Central venous access using a special device is necessary for the administration of Kovaltry. Use of such a device may be related with complications including: local infections, bacterial infection in the blood (bacteremia) and formation of blood clots in the blood vessels (thrombosis) at the catheter insertion site.

Children and adolescents

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

Test and follow-up

During the course of treatment with the preparation, it is highly recommended to perform laboratory blood tests at appropriate intervals to ensure that the dosage prescribed for you provides adequate factor VIII levels and that these levels are preserved.
In particular, in the case of major surgery, tight monitoring of the replacement therapy through coagulation tests is required.

Drug interactions

If you are taking, if you have recently taken, or if you might take, other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist.

Pregnancy, breastfeeding and fertility

There is no experience with use of factor VIII-containing medicines during pregnancy or when breastfeeding since type A hemophilia is rare among women.
If you are pregnant or breastfeeding, think you are pregnant or are planning to have a baby, consult the doctor before using the medicine.
Kovaltry is not likely to affect the fertility of women or men, as the active ingredient is naturally occurring in the body.

Driving and operating machinery

If you experience dizziness or other symptoms affecting your ability to concentrate or react, do not drive and do not operate machinery until this reaction subsides.
Children should be warned against riding a bicycle or playing near the road and the like.

Important information about some of the ingredients of the medicine

The medicine contains less than 1 mmol sodium (23 mg) per dose; therefore, it is considered essentially "sodium-free".

Documentation

It is recommended that the doctor record the name and lot number of the preparation each time Kovaltry is used.

3) HOW SHOULD YOU USE THE MEDICINE?

Treatment with Kovaltry will be started by a doctor who is experienced in the care of patients with type A hemophilia.
Always use the preparation according to the doctor's instructions. Check with the doctor or pharmacist if you are uncertain about the preparation dosage and treatment regimen.
The number of 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.

- Treatment duration
  The doctor will tell you how often and at what intervals to take Kovaltry.
  Usually, Kovaltry treatment is life-long.
- The medicine is intended for injection into a vein over 2-5 minutes, depending on the total volume injected and your comfort level. Use the preparation within 3 hours after reconstitution. From a microbiological perspective, the preparation should be used immediately after reconstitution.
- Use only the items (vial adapter, pre-filled syringe containing the solvent, infusion set) provided with each package of the preparation. Do not use if any component of the package is opened or damaged.
- After reconstitution and before use, the preparation must be filtered to clear it of particles that may be found in the solution. **The filtration is performed using the vial adapter.**
- Do not use the infusion set provided in the package to draw blood, as it contains an in-line filter.
- This medicine must **not** be mixed with other infusion solutions. Do not use a solution that contains particles or that looks cloudy. Carefully follow the instructions **and use the detailed instructions for reconstitution and use found at the end of this leaflet.**

If you accidentally took a higher dosage, refer to the doctor

There have been no reports of recombinant coagulation factor VIII overdose.
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 the medicine

- Inject the next dose immediately and continue with the injections at the usual intervals as recommended by your doctor.
- Do not inject a double dose to compensate for a forgotten dose.

Adhere to the treatment regimen as recommended by the doctor.

Do not stop treatment with the medicine without consulting with the doctor.

Do not take medicines in the dark! Check the label and the dose each time you take a medicine. Wear glasses if you need them.

If you have further questions regarding use of the medicine, consult the doctor.

4) SIDE EFFECTS

As with any medicine, use of Kovaltry may cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not suffer from any of them.
The most serious side effect is **allergic reaction**, which may be anaphylactic shock (an uncommon, severe allergic reaction that affects blood pressure and breathing). **If an allergic or anaphylactic reaction occurs, stop the injection/infusion immediately and speak to your doctor immediately.** Onset of any of the following symptoms during injection/infusion **could** be an early warning sign of an allergic or anaphylactic reaction:
- Chest tightness/general feeling of being unwell
- Dizziness
- Feeling faint upon standing indicating a slight reduction in blood pressure
- Nausea

For children not previously treated with factor VIII-containing preparations, 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). In such a case, the effect of the medicine may be reduced and you may experience persistent bleeding. If this happens, contact your doctor immediately.

Other side effects

Common side effects – effects that occur in up to 1 in 10 users
- Enlargement of lymph nodes (swelling under the skin of the neck, armpit or groin)
- Heart palpitations (feeling that the heart is beating strongly, rapidly, or irregularly)
- Rapid heartbeat
- Stomach pain or discomfort
- Indigestion
- Fever
- Local reactions where the medicine was injected (e.g., bleeding under the skin, intense itching, swelling, burning sensation, temporary redness)
- Headache
- Dizziness
- Sleeping difficulties
- Rash/itchy rash

Uncommon side effects – effects that occur in up to 1 in 100 users
- Strange taste in the mouth
- Urticaria (itchy rash)
- Flushing (redness of the face)

If a side effect occurs, 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 link "Report Side Effects of Drug Treatment" found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link:
https://sideeffects.health.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 and sight of children and/or infants in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.
- Do not use the medicine after the expiry date (exp. date) that appears on the package. The expiry date refers to the last day of that month.
- Store refrigerated (2°C-8°C: this is the temperature range in most household refrigerators). Do not freeze. Store the medicine in the original package to protect from light.
  The medicine can be stored at room temperature (up to 25°C) in the outer box for a period limited to 12 months. If you store the medicine at room temperature, the expiry of the medicine will be 12 months from the day it was taken out of refrigeration or the expiry date indicated on the package, the earlier of the two. The new expiry date must be noted on the outer box.
- After reconstitution, **do not** refrigerate the solution. Use the preparation within 3 hours of reconstitution. From a microbiological perspective, the preparation should be used immediately after reconstitution. This preparation is for single use only. Dispose of the unused remnants of the solution.
- Do not use the preparation if you notice particles or if the solution is cloudy.
- Do not discard of medicines in the household waste or waste bin. Consult a pharmacist as to how to dispose of medicines you no longer need. This will help protect the environment.

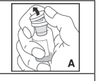
6) FURTHER INFORMATION

- 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 injection
  The medicine contains less than 1 mmol sodium (23 mg) per dose (see in section 2 "Important information about some of the ingredients of the medicine").
- What does the medicine look like and what are the contents of the package?
  Kovaltry is provided as a kit comprising a powder and solvent for solution for injection. The powder is dry, white to yellow. The solution obtained after reconstitution is clear.
  Each package of Kovaltry contains a vial with powder and a pre-filled syringe with solvent, a separate plunger. It also contains a vial adapter and an infusion set (for injection into the vein).
  The items needed for reconstitution and injection are provided with each package of the preparation.
- Registration Holder and Address: Bayer Israel Ltd., 36 Hacharash St., Hod Hasharon 45240.
- Manufacturer and Address: Bayer A.G., Leverkusen, Germany.
- Revised in October 2020
- 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 the vial and vial adapter:

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

1.	Wash your hands thoroughly using soap and warm water.	
2.	Warm an unopened vial and the syringe in your hands to a comfortable temperature (no more than 37°C).	
3.	Remove the cap from the vial **(A)**, wipe the rubber stopper with an alcohol swab and let it air-dry before use.	
4.	Place **the vial** on a firm, non-slip surface. Peel off the paper cover on the plastic housing of the vial adapter. **Do not** remove the adapter from the plastic housing. Holding the adapter through the plastic housing, place it over the vial containing the powder and firmly place it on the opening of the vial **(B)**. The adapter will now attach to the vial. **Do not** remove the adapter plastic housing at this point.	
5.	Hold the pre-filled syringe upright. Grasp the syringe plunger as per the picture and attach the plunger by firmly turning it clockwise into the threaded stopper **(C)**.	
6.	Holding the syringe by the barrel, snap the cap at the tip **(D)**. Do not touch the syringe tip with your hand or allow it to contact 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 on to the adapter by turning clockwise **(F)**.	
9.	Inject the solvent by slowly pushing down on the syringe plunger **(G)**.	
10.	Swirl the vial gently until all the powder preparation is dissolved **(H)**. Do not shake the vial. Be sure that the powder is completely dissolved. Before use, visually inspect the solution for particles or discoloration. Do not use solutions containing visible particles or cloudy solutions.	
11.	Hold the vial with the opening facing down and above the adapter and syringe **(I)**. Fill the syringe by drawing the syringe plunger out slowly and smoothly. Ensure that the full 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.	Holding the vial 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 tourniquet.	
17.	Inject the solution into a vein over 2-5 minutes, keeping an eye on the position of the needle. The speed of injection should be based on the patient's comfort, but should not be faster than 2 mL per minute.	
18.	If an injection of a further dose is needed, use a new syringe with reconstituted powder as described above.	
19.	If an injection of a further dose is not required, remove the infusion set and syringe. Hold a pad firmly over the injection site, with the patient's arm outstretched for about 2 minutes. Finally, apply mild pressure on the injection site and consider if a plaster is necessary.	