Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986
This medicine is dispensed with a doctor's prescription only

Refixia 1000 IU
Powder and solvent for solution for injection

Active ingredient:
nonacog beta pegol

Pegylated human coagulation factor IX (rDNA). Each vial of Refixia contains nominally 1000 IU nonacog beta pegol, corresponding to approximately 250 IU/ml after reconstitution with histidine solvent.

Inactive ingredients and allergens: See section 2 '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 you. Do not pass it on to others. It may harm them, even if it seems to you that their medical condition is similar to yours.

1. What is this medicine intended for?

Refixia is indicated for treatment and prophylaxis of bleeding in pretreated patients with haemophilia B (congenital factor IX deficiency).

Therapeutic group: antihaemorrhagics, coagulation factor IX.
Refixia contains the active substance nonacog beta pegol. It is a long-acting version of factor IX.

Factor IX is a protein naturally found in the blood, which helps to stop bleeding.
In patients with haemophilia B, factor IX is missing or does not work properly. Refixia replaces the faulty or missing factor IX and helps to form blood clots at the site of bleeding.

2. Before using this medicine

Do not use this medicine if:

- You are sensitive (allergic) to the active substance or to any of the other ingredients in this medicine (see section 6).
- You are allergic to hamster proteins.

Special warnings about using this medicine

Talk to your doctor before using Refixia.

Allergic reactions and development of inhibitors
There is a rare risk that you may experience a sudden and severe allergic reaction (e.g. anaphylactic reaction) to Refixia. Stop the injection and contact your doctor or an emergency room immediately if you have signs of an allergic reaction, such as rash, hives, weals, itching of large areas of skin, redness and/or swelling of lips, tongue, face or hands, difficulty in swallowing or breathing, shortness of breath, wheezing, tightness of the chest, pale and cold skin, fast heartbeat, and/or dizziness.

Your doctor may need to treat you promptly for these reactions. Your doctor may also carry out a blood test to check if you have developed factor IX inhibitors (neutralising antibodies against your medicine), as inhibitors may develop together with allergic reactions. If you have such inhibitors, you may have a higher risk of sudden and severe allergic reactions (e.g. anaphylactic reaction) during future treatment with factor IX.
Because of the risk of allergic reactions during factor IX administration, your initial treatment with Refixia should be given in a medical clinic or in the presence of health care professionals, where proper medical care for allergic reactions can be provided, if needed.

Talk to your doctor immediately if your bleeding does not stop as expected or if you have to significantly increase the amount of Refixia you need to stop a bleed. Your doctor will perform a blood test to check if you have developed inhibitors (neutralising antibodies) against Refixia. The risk for developing inhibitors is highest in people who have not been treated with factor IX medicines in the past, typically small children.

Blood clots
Tell your doctor if any of the following apply to you, as there is an increased risk of blood clots during treatment with Refixia:
1. You have recently had surgery
2. You suffer from other serious illness e.g. liver disease, heart disease, or cancer
3. You have risk factors for heart disease, e.g. high blood pressure, obesity, or smoking.

Kidney disorder (nephrotic syndrome)
There is a rare risk of developing a specific kidney disorder called “nephrotic syndrome” following high doses of factor IX in haemophilia B patients with factor IX inhibitors and a history of allergic reactions.

Catheter-related problems
If you have a central venous access device (CVAD), you may develop infections or blood clots at the site of the catheter.

Drug interactions

If you are taking or have recently taken other medicines, including non-prescription medications and dietary supplements, tell your doctor or pharmacist.

Pregnancy and breastfeeding
Information regarding the use of Refixia during pregnancy and breastfeeding is not available.
If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using Refixia.

Driving and using machines
Refixia has no or negligible influence on the ability to drive and use machines.

Important information about some of this medicine’s ingredients
This medicine contains less than 1 mmol (23 mg) sodium per vial, that is to say essentially “sodium-free”. In case of treatment with several vials, the total sodium content should be taken into account.

3. How to use this medicine?

Treatment with Refixia will be started by a doctor who is experienced in the care of patients with haemophilia B. Always use this medicine according to your doctor's instructions. Check with your doctor or pharmacist if you are not sure about your dose or about how to use this medicine.
Only your doctor will determine your dose and how you should use this medicine.

Your doctor will calculate the suitable dose for you, depending on your weight and the purpose of using the medicine.

The recommended dosage is usually:
Prevention of bleeding
The usual dose of Refixia is 40 international units (IU) per kg of body weight. This dose is given as one injection every week. Your doctor may choose another dose or change how often the injections should be given, based on your need.

Treatment of bleeding
The usual dose of Refixia is 40 international units (IU) per kg of body weight. Depending on the location and the severity of bleeding, you may need a higher dose (80 IU per kg) or extra injections. Discuss with your doctor the dose and number of injections you need.

Do not exceed the recommended dose.

Use in children and adolescents
The recommended dose for children is the same as for adults: 40 international units (IU) per kg of body weight.

How Refixia is given
Refixia is available as powder and solvent for solution preparation (reconstitution), and is given as an injection into a vein. See “Instructions on how to use Refixia” for more information.

If you have accidentally taken a higher dose
If you use more Refixia than you should, contact your doctor.

If you have to significantly increase the amount of Refixia you need to stop a bleed, talk to your doctor immediately. For further information, see section 2 “Allergic reactions and development of inhibitors”.

If you forget to use the medicine
If you forget a dose, inject the missed dose as soon as you remember. Do not inject a double dose to make up for a forgotten dose. If you are in doubt, contact your doctor.
Adhere to the treatment as recommended by your doctor.

If you stop using the medicine
If you stop using Refixia, you may no longer be protected against bleeding or a current bleed may not stop.
Even if your health improves, do not stop taking this medicine without consulting your doctor.

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

4. Side effects
Like with all medicines, using Refixia 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 following side effects may occur while using this medicine.

Allergic reactions may occur during treatment with this medicine.
If sudden and severe allergic reactions (e.g. anaphylactic reactions) occur, the injection must be stopped immediately. You must contact your doctor or an emergency room immediately if you have early signs of a severe allergic reaction (anaphylactic reaction) such as:
- difficulty in swallowing or breathing
- shortness of breath or wheezing

- chest tightness
- redness and/or swelling of the lips, tongue, face or hands
- rash, hives, weals or itching
- pale and cold skin, fast heartbeat, and/or dizziness (low blood pressure).

Additional side effects

Common side effects – effects that affect up to one in ten users
- itching
- skin reactions at the injection site
- nausea
- feeling very tired.

Uncommon side effects – effects that affect up to one in one hundred users
- allergic reactions (hypersensitivity). These reactions may become severe and could be life-threatening (anaphylactic reactions)
- heart palpitations
- hot flushes.

Side effects of unknown frequency (the frequency of these effects has not been established yet)
- neutralising antibodies (inhibitors)
- anaphylactic reactions.

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 and on the vial and the pre-filled syringe labels. The expiry date refers to the last day of that month.

Storage conditions:
- Store in a refrigerator (2°C–8°C). Do not freeze. Store the vial in the outer package in order to protect from light.
- The medicine may be taken out of the refrigerator for a maximum period of 6 months and stored at room temperature (up to 30°C). Please record on the carton the date on which Refixia was removed from the refrigerator for storage at room temperature. The new expiry date should never exceed the one initially mentioned on the outer carton. If the medicine has not been used before the new expiry date, it should be disposed of. After storage at room temperature, the medicine must not be returned to the refrigerator.
- Use the solution for injection immediately after preparation (reconstitution). If it cannot be used immediately, use it within 24 hours if stored in a refrigerator at 2°C–8°C or within 4 hours if stored out of the refrigerator at a maximum temperature of 30°C.
- The powder in the vial is white to off-white. Do not use the powder if its colour has changed.
- The reconstituted solution should be clear and colourless to slightly yellow. Do not use the reconstituted solution if you notice any particles or discolouration.
- Do not throw away any medicine via wastewater or household waste. Ask your 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, this medicine also contains:

- In the powder:

Mannitol, sucrose, sodium chloride, histidine, polysorbate 80, sodium hydroxide, hydrochloric acid and water for injections.

- In the solvent:

Histidine and water for injections.

What the medicine looks like and contents of the pack:

- Refixia is provided as a powder and solvent for solution for injection (powder containing 1000 IU in a vial and 4 ml solvent in a pre-filled syringe, a plunger rod with a vial adapter) .
- The powder is white to off-white and the solvent is clear and colourless.

Registration holder's name and address:

Novo Nordisk Ltd.
1 Atir Yeda St.,
Kfar Saba 4464301

Manufacturer's name and address:

Novo Nordisk A.S.,
Novo Alle, DK-2880 Bagsværd, Denmark

Approved in 05/2023

Registration number of the medicine in the National Drug Registry of the Ministry of Health:
Refixia 1000 IU 172-35-37303-00

Instructions on how to use Refixia

Read these instructions carefully before using Refixia.

Refixia is supplied as a powder. Before injection, a solution must be prepared (reconstituted) with the solvent supplied in the syringe. The solvent is a histidine solution. The reconstituted solution must be injected into a vein (intravenous (IV) injection). The equipment in this package is designed to reconstitute and inject Refixia.

You will also need an infusion set (tubing and butterfly needle), sterile alcohol swabs, gauze pads and plasters. These items are not included in the Refixia package.

Do not use the equipment without proper training by your doctor or nurse.

Always wash your hands and ensure that your environment is clean.

When you prepare a medicine and inject it directly into the vein, it is important to **use a clean and germ-free (aseptic) technique.** Incorrect technique may introduce germs that can infect the blood.

Do not open the equipment until you are ready to use it.

Do not use the equipment if it has been dropped, or if it is damaged. Use a new package instead.

Do not use the equipment if it has expired. Use a new package instead. The expiry date is printed on the outer carton, on the vial, on the vial adapter, and on the pre-filled syringe.

Do not use the equipment if you suspect it is contaminated. Use a new package instead.

Do not dispose of any of the items until after you have injected the reconstituted solution.

The equipment is for single use only.

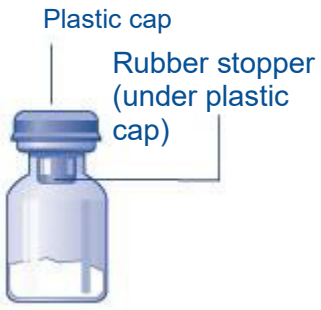
Contents

The package contains:

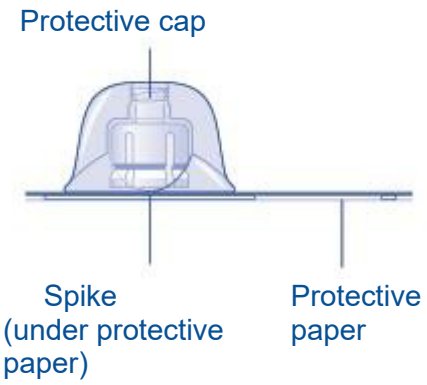
- 1 vial with Refixia powder
- 1 vial adapter
- 1 pre-filled syringe with solvent
- 1 plunger rod (placed under the syringe)

General overview

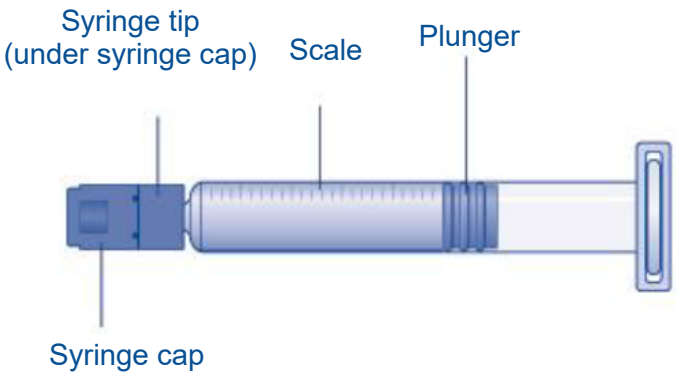
Vial with Refixia powder

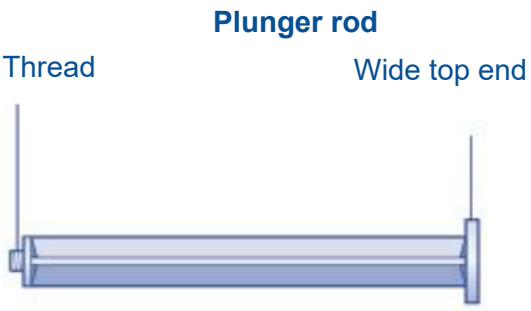


Vial adapter



Pre-filled syringe with solvent





1. Prepare the vial and the syringe

- **Take out the number of Refixia packages you need.**
- **Check the expiry date.**
- **Check the name, strength and colour** of the package to make sure it contains the correct product.
- **Wash your hands** and dry them properly using a clean towel or air dry.
- Take the vial, the vial adapter and the prefilled syringe out of the carton. **Leave the plunger rod untouched in the carton.**
- **Bring the vial and the pre-filled syringe to room temperature.** You can do this by holding them in your hands until they feel as warm as your hands.
- **Do not use any other way to warm** the vial and pre-filled syringe.

- **Remove the plastic cap** from the vial**. If the plastic cap is loose or missing, do not use the vial.**
- **Wipe the rubber stopper with a sterile alcohol swab** and allow it to air dry for a few seconds to ensure that it is as germ-free as possible.
- **Do not touch the rubber stopper with your fingers as this can transfer germs.**

2. Attach the vial adapter

- **Remove the protective paper from the vial adapter.**

  If the protective paper is not fully sealed or if it is broken, do not use the vial adapter.

  Do not take the vial adapter out of the protective cap with your fingers. If you touch the spike on the vial adapter, germs from your fingers may be transferred.

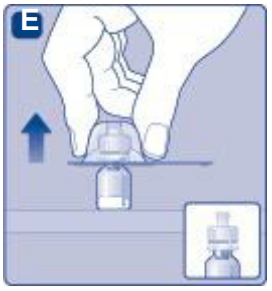
- **Place the vial on a flat and solid surface.**
- **Turn over the protective cap,** and snap the vial adapter onto the vial.

  Once attached, do not remove the vial adapter from the vial.

- **Gently squeeze the protective cap** with your thumb and index finger as shown in the figure.

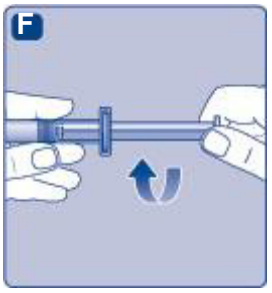
  Remove the protective cap from the vial adapter.

  Do not lift the vial adapter from the vial when removing the protective cap.



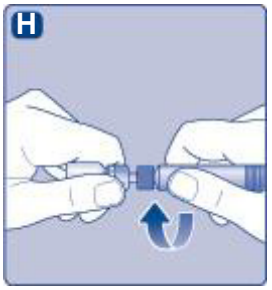
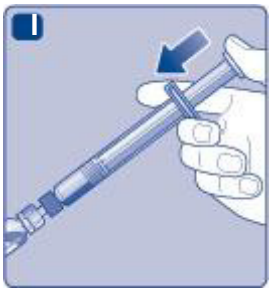
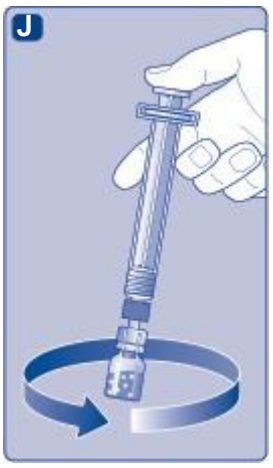
3. Attach the plunger rod and the syringe

- Grasp the plunger rod by the wide top end and take it out of the carton. **Do not touch the sides or the thread of the plunger rod.** If you touch the sides or the thread, germs from your fingers may be transferred.
- **Immediately** connect the plunger rod to the syringe by turning it clockwise into the plunger inside the pre-filled syringe until resistance is felt.



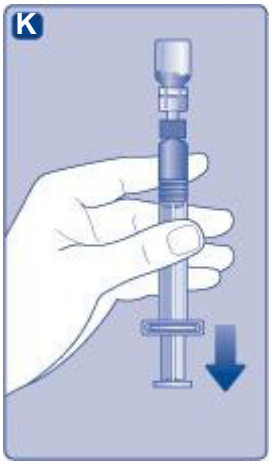
- **Remove the syringe cap** from the pre-filled syringe by bending it down until the perforation breaks.
- **Do not touch the syringe tip under the syringe cap.** If you touch the syringe tip, germs from your fingers may be transferred.

  If the syringe cap is loose or missing, do

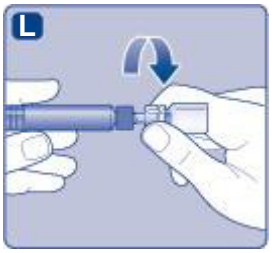
not use the pre-filled syringe.	
• **Screw the pre-filled syringe securely** onto the vial adapter until resistance is felt.	
4. Reconstitute the powder with the solvent • **Hold the pre-filled syringe slightly tilted** with the vial pointing downwards. • **Push the plunger rod** to inject all the solvent into the vial.	
• **Keep the plunger rod pressed down and swirl** the vial gently until all the powder is dissolved. **Do not shake the vial as this will cause foaming.** • **Check the reconstituted solution.** It must be clear and colourless to slightly yellow, and no particles should be visible. **If you notice particles or discolouration, do not use the solution.** Use a new package instead.	
Refixia is recommended to be used immediately after it has been reconstituted. This is because if left unused, the medicine may no longer be sterile and could cause infections. **If you cannot use the reconstituted Refixia solution immediately,** it should be used within 4 hours when stored at room temperature (up to 30°C) and within 24 hours when stored in a refrigerator (2°C – 8°C). Store the reconstituted product in the vial. **Do not freeze reconstituted Refixia solution or store it in syringes.** **Keep reconstituted Refixia solution out of direct light.** ⓘ If your dose requires more than one vial, repeat steps **A** to **J** with additional vials, vial adapters and pre-filled syringes until you have reached your required dose.	

- **Keep the plunger rod pushed completely in.**
- **Turn the syringe** with the vial upside down.
- **Stop pushing the plunger rod and let it move back** on its own while the reconstituted solution fills the syringe.
- **Pull the plunger rod gently downwards** to draw the reconstituted solution into the syringe.
- **If you only need a part of the entire vial, use the scale on the syringe to determine how much reconstituted solution you should withdraw, as instructed by your doctor or nurse.**

  If, at any point, there is air in the syringe, inject the air back into the vial.
- While holding the vial upside down, **tap the syringe gently** to let any air bubbles rise to the top.
- **Push the plunger rod** slowly until all air bubbles are gone.



- **Unscrew the vial adapter** with the vial.
- **Do not touch the syringe tip.** If you touch the syringe tip, germs from your fingers may be transferred.



5. Inject the reconstituted solution

Refixia is now ready for injection into your vein.
- Inject the reconstituted solution as instructed by your doctor or nurse.
- Inject slowly over 1 to 3 minutes.
- Do not mix Refixia with any other intravenous infusions or medicines.

Injecting Refixia via needleless connectors for intravenous (IV) catheters

Caution: The pre-filled syringe is made of glass and is designed to be compatible with standard luer-lock connections. Some needleless connectors with an internal spike are incompatible with the pre-filled syringe. This incompatibility may prevent administration of the medicine and/or result in damage to the needleless connector.

Injecting the solution via a central venous access device (CVAD) such as a central venous catheter or a subcutaneous port:
- Use a clean and germ-free (aseptic) technique. Follow the instructions for proper use for your connector and CVAD in consultation with your doctor or nurse.
- Injecting into a CVAD may require using a sterile 10 ml plastic syringe for withdrawal of the reconstituted solution. This should be done immediately after step J.

- If the CVAD line needs to be flushed before or after Refixia injection, use sodium chloride 9 mg/ml solution for injection.

Disposal

- **After injection, safely dispose** of all unused Refixia solution, the syringe with the infusion set, the vial with the vial adapter and other waste materials as instructed by your pharmacist.

  Do not discard the items into the household waste.

Do not disassemble the equipment before disposal.

Do not reuse the equipment.