Package leaflet: Information for the patient

VEYVONDI 650 IU powder and solvent for solution for injection
VEYVONDI 1300 IU powder and solvent for solution for injection
vonicog alfa

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What VEYVONDI is and what it is used for

VEYVONDI contains the active substance vonicog alfa, which is a recombinant human von Willebrand factor (rVWF). It behaves in the same way as natural human von Willebrand factor (VWF) in the body. VWF is the carrier molecule for coagulation factor VIII and is involved in blood clotting making platelets stick to wounds and so helps to form a blood clot. Lack of VWF increases the tendency to bleed.

VEYVONDI is used to prevent and treat bleeding episodes, including bleeding during surgery in adult patients (aged 18 years and older) with von Willebrand disease. It is used when treatment with another medicine, desmopressin, is not effective or cannot be given.

Von Willebrand disease is an inherited bleeding disorder caused by the lack or an insufficient amount of von Willebrand factor. In patients with the disease the blood does not clot normally leading to a prolonged bleeding time. Administration of von Willebrand factor (VWF) allows for correction of von Willebrand factor deficiency.

2. What you need to know before you use VEYVONDI

Do not use VEYVONDI
- if you are allergic to vonicog alfa or any of the other ingredients of this medicine (listed in section 6)
- if you are allergic to mouse or hamster proteins

If you are unsure about this, ask your doctor.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using VEYVONDI.

There is a risk that you may experience a hypersensitivity reaction (a severe, sudden allergic reaction) to VEYVONDI. Your doctor should inform you about early signs of severe allergic reactions such as increased heart rate, rash, hives, wheals, generalised itching, swelling of lips and tongue, difficulty in breathing, wheezing, tightness in the chest, fast heartbeat, stuffy nose, red eyes,general feeling of being unwell, and dizziness. These could be early symptoms of a hypersensitivity reaction. **If any of these symptoms occur, stop the infusion immediately and contact your doctor. Severe symptoms, including difficulty in breathing and dizziness, require prompt emergency treatment.**

Patients developing inhibitors
Inhibitors (antibodies) against the VWF may occur in some patients receiving the medicine.These inhibitors, especially at high levels, could cause the treatment to stop working properly. You will be monitored carefully for the possibility of having developed these inhibitors.
- If your bleeding is not controlled with VEYVONDI, tell your doctor immediately.

If your plasma VWF or factor VIII fail to reach the expected levels with VEYVONDI based on the test results followed by your doctor, or if bleeding is not adequately controlled, it could be due to the presence of VWF or factor VIII antibodies. This will be checked by your doctor. You might need a higher dose of VEYVONDI, or a higher dose of factor VIII, or even a different medicine to control bleedings. Do not increase the total dose of VEYVONDI to control your bleeding without consulting your doctor.

If you have previously been treated with plasma-derived VWF concentrates you may have reduced response to VEYVONDI due to pre-existing antibodies. Your doctor may adjust the dose according to your laboratory results.

Thrombolism and embolism
There is a risk of occurrence of thrombotic events if you have known clinical or laboratory risk factors. Therefore your doctor will monitor you for early signs of thrombosis.

FVIII products may contain varying amounts of VWF. Therefore, any FVIII product that would be administered in combination with VEYVONDI should be a pure FVIII product.

If you previously had problems with blood clots or vessel occlusion (thromboembolic complications), tell your doctor immediately.

Children and adolescents

VEYVONDI is not approved for use in children or adolescents below 18 years.

Other medicines and VEYVONDI

Tell your doctor, pharmacist or nurse if you are using, have recently used or might use any other medicines.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor, pharmacist or nurse for advice before taking this medicine.

Driving and using machines

VEYVONDI is not likely to affect your ability to drive and use machines.

VEYVONDI contains sodium

This medicine contains 5.2 mg sodium (main component of cooking/table salt) in each 650 IU vial or 10.4 mg sodium in each 1300 IU vial.

This is equivalent to 2.2% of the recommended maximum daily dietary intake of sodium for an adult, assuming 70 kg body weight and 80 IU/kg body weight.

This should be taken into consideration if you are on a controlled sodium diet.

3. How to use VEYVONDI

Your treatment with VEYVONDI will be supervised by a doctor who is experienced in the care of patients with von Willebrand disease.

Your doctor will calculate your dose of VEYVONDI (in international units or IU). The dose depends on:
- body weight,
- the site of the bleeding
- intensity of the bleeding,
- your clinical condition,
- the required surgery
- the VWF activity levels in your blood after surgery
- the severity of your disease

Your doctor may test your blood to make sure that you have adequate levels of von Willebrand factor. This is particularly important if you are having major surgery.

Treatment of bleeding episodes
Your doctor will calculate the dose that is most appropriate for you, how often you should receive VEYVONDI and for how long.

For minor bleeding (e.g. nose bleed, oral bleeding, menorrhagia), each initial dose is usually 40 to 50 IU/kg and for major bleeding (severe or refractory nose bleed, menorrhagia, gastrointestinal bleeding, Central nervous system trauma, haemarthrosis, or traumatic haemorrhage), each initial dose is 50 to 80 IU/kg. Subsequent doses (as clinically required) are 40 to 50 IU/kg every 8 to 24 hours for minor bleeds as long as deemed clinically necessary and for major bleeds 40 to 60 IU/kg for approximately 2-3 days.

If you feel that VEYVONDI is not working well enough, talk to your doctor. Your doctor will perform tests to make sure that you have adequate levels of von Willebrand factor. If you use VEYVONDI at home, your doctor will make sure that you are shown how to infuse it and how much to use.

Prevention of bleeding in case of elective surgery
For prevention of excessive bleeding your doctor will assess the FVIII:C levels within 3 hours before surgery. If your FVIII level is inadequate your doctor may give you a dose of 40-60 IU/kg VEYVONDI 12-24 hours (pre-operative dose) prior to initiating elective surgery in order to raise FVIII levels to the target level (0.4 IU/mL for minor and at least 0.8 IU/mL for major surgery). Within 1 hour prior to surgery, you will receive a dose of VEYVONDI based on the assessment 3 hours before surgery. The dose depends on VWF and FVIII levels of the patient, the type and severity of the expected bleeding.

Prophylaxis treatment
The usual starting dose for long term prophylaxis against bleeding episodes is 40 to 60 IU/kg twice weekly. The dose can be adjusted to a maximum of 80 IU/kg one to three times per week, depending on your condition and how well VEYVONDI is working for you. Your doctor will calculate the dose that is most appropriate for you, how often you should receive VEYVONDI and for how long.

How VEYVONDI is given

VEYVONDI is usually infused into a vein (intravenously) by your doctor or nurse. Detailed instructions for reconstitution and administration are given at the end of this package leaflet.

Use in children and adolescents

VEYVONDI is not approved for use in children and adolescents below 18 years.

If you use more VEYVONDI than you should

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. If you infuse more VEYVONDI than recommended, tell your doctor as soon as possible. There may be a risk of developing blood clots (thrombosis) in case of an accidental high dose.

If you forget to use VEYVONDI

- Do not infuse a double dose to make up for a forgotten dose.
- Proceed with the next infusion as scheduled and continue as advised by your doctor.

If you stop using VEYVONDI

Do not stop using VEYVONDI without consulting your doctor.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine may cause side effects, although not everybody gets them.

You can have a serious allergic reaction to VEYVONDI.

You must **stop the infusion** and **contact your doctor immediately** if you have any of the following early symptoms of severe allergic reactions:
- rash or hives, itching all over the body,
- tightness of the throat, chest pain or chest tightness,
- difficulty breathing, light headedness, fast heartbeat,
- dizziness, nausea or fainting.

The following side effects have been reported with VEYVONDI:

Very common (may affect more than 1 in 10 people)

- headache

Common (may affect up to 1 in 10 people)
- nausea
- vomiting
- tingling or burning at infusion site
- chest discomfort
- dizziness
- vertigo
- blood clots
- hot flushes
- itching
- high blood pressure
- muscle twitching
- unusual taste
- increased heart rate

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store VEYVONDI

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and the vial label after EXP. The expiry date refers to the last day of that month.
- Store below 30 °C.
- Do not freeze.
- Store in the original package in order to protect from light.
- Do not refrigerate the solution after preparation.
- Use the reconstituted product within 3 hours to avoid the risk of microbial contamination, because the product does not contain preservatives.
- This medicine is for single use only. Discard any unused solution appropriately.
- 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.

6. Contents of the pack and other information

What VEYVONDI contains

The active substance is vonicog alfa (recombinant human von Willebrand factor).

VEYVONDI 650 IU powder and solvent for solution for injection
Each vial of powder contains nominally 650 International Units (IU) vonicog alfa.
After reconstitution with the 5 mL solvent provided, VEYVONDI contains approximately 130 IU/mL vonicog alfa.

VEYVONDI 1300 IU powder and solvent for solution for injection

Each vial of powder contains nominally 1300 International Units (IU) vonicog alfa.
After reconstitution with the 10 mL solvent provided, VEYVONDI contains approximately 130 IU/mL vonicog alfa.

The other ingredients are:

- Sodium citrate, glycine, trehalose dihydrate, mannitol, polysorbate 80 and water for injections.
- See section 2 "VEYVONDI contains sodium".

What VEYVONDI looks like and contents of the pack
VEYVONDI is a white to off-white powder. After reconstitution, when drawn into the syringe, the solution is clear, colourless in appearance and free from flakes or other foreign particles.

Each pack of VEYVONDI 650 IU contains:
- powder in a glass vial with a rubber stopper
- 5 mL of solvent in a glass vial with a rubber stopper
- one reconstitution device (Mix2Vial)

Each pack of VEYVONDI 1300 IU contains:
- powder in a glass vial with a rubber stopper
- 10 mL of solvent in a glass vial with a rubber stopper
- one reconstitution device (Mix2Vial)

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Instructions for preparation and administration

General instructions

Check the expiry date, and ensure that the VEYVONDI powder and water for injections (solvent) are at room temperature prior to preparation. Do not use after the expiry date stated on the labels and carton.

Use antiseptic technique (clean and low-germ conditions) and a flat work surface during the reconstitution procedure. Wash your hands and put on clean exam gloves (the use of gloves is optional).

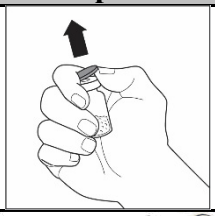
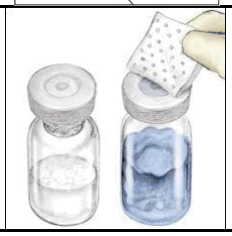
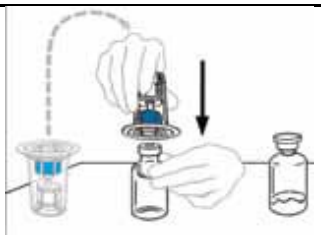
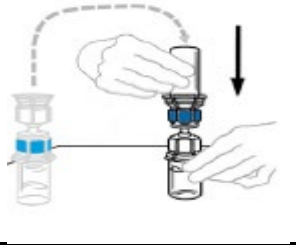
Use the reconstituted product (after mixing the powder with the supplied water) as soon as possible and within three hours. You can store the reconstituted product at room temperature not to exceed 25 °C for up to three hours. Reconstituted product should not be refrigerated. Discard after three hours.

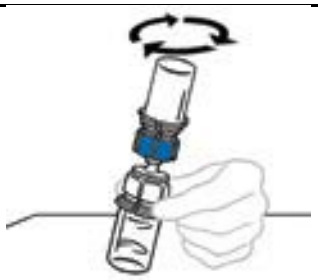
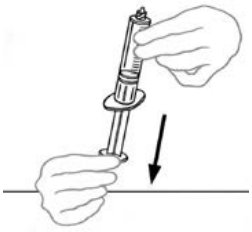
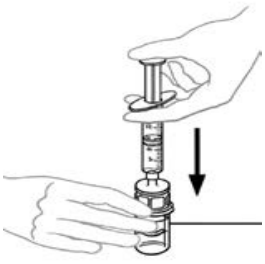
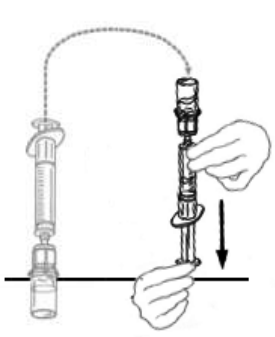
Ensure that the VEYVONDI powder vial and the Sterilised Water for Injections (solvent) are at room temperature prior to preparation.

Use plastic syringes with this product because proteins in the product tend to stick to the surface of glass syringes.

Do not mix VEYVONDI with other medicinal products except for octocog alfa (ADVATE).

Instructions for reconstitution

	Steps	Image example
1	Remove the caps from the VEYVONDI powder and solvent vials to expose the centre of the rubber stoppers.	
2	Disinfect each stopper with a separate sterile alcohol swab (or other suitable sterile solution suggested by your doctor or haemophilia treatment centre) by wiping the stopper for several seconds. Allow the rubber stoppers to dry. Place the vials on a flat surface.	
3	Open the Mix2Vial device package by completely peeling away the lid, without touching the inside of the package. Do not remove the Mix2Vial device from the package.	NA
4	Turn the package with the Mix2Vial device upside down and place it over the top of the solvent vial. Firmly insert the blue plastic spike of the device into the centre of the solvent vial stopper by pushing straight down. Grip the package at its edge and lift it off the Mix2Vial device. Be careful not to touch the clear plastic spike. The solvent vial now has the Mix2Vial device connected to it and is ready to be connected to the VEYVONDI vial.	
5	To connect the solvent vial to the VEYVONDI vial, turn the solvent vial over and place it on top of the vial containing VEYVONDI concentrate. Fully insert the clear plastic spike into the VEYVONDI vial stopper by firmly pushing straight down. This should be done right away to keep the liquid free of germs. The solvent will flow into the VEYVONDI vial by vacuum. Check that all the solvent has transferred. Do not use if vacuum has been lost and the solvent does not flow into the VEYVONDI vial.	

6	Gently and continuously swirl the connected vials or allow the reconstituted product to stand for 5 minutes then gently swirl to ensure the powder is completely dissolved. Do not shake. Shaking will adversely affect the product. Do not refrigerate after reconstitution.	
7	Disconnect the two sides of the Mix2Vial from each other by holding the clear plastic side of the Mix2Vial device attached to the VEYVONDI vial with one hand and the blue plastic side of the Mix2Vial device attached to the solvent vial with the other hand. Turn the blue plastic side counterclockwise and gently pull the two vials apart. Do not touch the end of the plastic connector attached to the VEYVONDI vial containing the dissolved product. Place the VEYVONDI vial on a flat work surface. Discard the empty solvent vial.	
8	Draw air into the empty, sterile disposable plastic syringe by pulling back on the plunger. The amount of air should equal the amount of reconstituted VEYVONDI that you will withdraw from the vial.	
9	Leaving the VEYVONDI vial (containing the dissolved product) on your flat work surface, connect the syringe to the clear plastic connector by attaching and turning the syringe clockwise.	
10	Hold the vial with one hand and use the other hand to push all the air from the syringe into the vial	
11	Flip connected syringe and VEYVONDI vial so the vial is on top. Be sure to keep the syringe plunger pressed in. Draw the VEYVONDI into the syringe by pulling plunger back slowly.	

12	Do not push and pull solution back and forth between syringe and vial. Doing so may harm the medicine. When ready to infuse, disconnect the syringe by turning it counterclockwise. Inspect the syringe visually for particulate matter; the solution in the syringe should be clear. If flakes or particles are seen, do not use the solution and notify your doctor.	
13	If you need more than one vial of VEYVONDI to make up your dose: • Leave the syringe attached to the vial until an additional vial is prepared. • Use the reconstitution steps above (2 to 8) to prepare the additional vial of VEYVONDI using a fresh Mix2Vial for each vial	
14	The contents of two vials may be drawn into a single syringe. **NOTE:** When pushing air into a second vial of VEYVONDI to be pooled into a syringe, position the vial and connected syringe so that the vial is on top.	

Instructions for administration

Inspect the prepared solution in the syringe for particulate matter and discoloration prior to administration (the solution should be clear, colourless and free from particles). It is not uncommon for a few flakes or particles to remain in the **product vial after reconstitution**. The filter included in the Mix2Vial device removes those particles completely. Filtration does not influence dose calculations. **The solution in the syringe** should not be used if it is cloudy or contains flakes or particles after filtration.

1. Attach the infusion needle to a syringe containing VEYVONDI solution. For comfort, a winged (butterfly) infusion set is preferred. Point the needle up and remove any air bubbles by gently tapping the syringe with your finger and slowly and carefully pushing air out of the syringe and needle.
2. Apply a tourniquet and get the infusion site ready by wiping the skin well with a sterile alcohol swab (or other suitable sterile solution suggested by your doctor or haemophilia treatment centre).
3. Insert the needle into the vein and remove the tourniquet. Slowly infuse VEYVONDI. Do not infuse any faster than 4 mL per minute. Disconnect the empty syringe. If your dose requires multiple syringes, attach and administer each additional syringe of VEYVONDI one at a time.
   Note:
   Do not remove butterfly needle until all syringes have been infused and do not touch the Luer port that connects to the syringe.
   If recombinant factor VIII has been prescribed, administer recombinant factor VIII within 10 minutes after infusion of VEYVONDI has been completed.
4. Take the needle out of the vein and use sterile gauze to put pressure on the infusion site for several minutes.

In case large volumes of VEYVONDI are required, it is possible to pool two vials of VEYVONDI together. The contents of each reconstituted product of VEYVONDI can be drawn in a single syringe. However, in these cases the initially reconstituted solution should not be diluted any further.
Do not recap the needle. Place the needle, syringe, and empty VEYVONDI and solvent vial(s) in a hard-walled sharps container for proper disposal. Do not dispose of these supplies in ordinary household trash**.**

The following information is intended for healthcare professionals only:

Treatment of bleeding episodes (On-demand treatment)

Dose and frequency must be individualized based on clinical judgment, taking into account of severity of bleeding episode, site of bleeding, patient's medical history, monitoring of appropriate clinical and laboratory measures (both VWF:RCo and FVIII:C levels).

Start of treatment

VEYVONDI should be administered with recombinant factor VIII if the FVIII:C levels are <40%, or are unknown, to control bleeding. The rFVIII dose should be calculated according to the difference between the patient's baseline plasma FVIII:C level, and the desired peak FVIII:C level to achieve an appropriate plasma FVIII:C level based on the approximate mean recovery of 0.02 (IU/mL)/(IU/kg). The complete dose of VEYVONDI should be administered followed by rFVIII within 10 minutes.

Calculating dose

VEYVONDI dose [IU] = dose [IU/kg] x body weight [kg]

Subsequent infusions

Administer a subsequent dose of 40 IU to 60 IU/kg of VEYVONDI infused every 8 to 24 hours as per the dosing ranges in Table 1, as long as clinically required. In major bleeding episodes, maintain trough levels of VWF:RCo greater than 50% for as long as deemed necessary.

Table 1.
Dosing recommendations for the treatment of minor and major haemorrhages

Haemorrhage	**Initial dose [a] (IU VWF:RCo/kg body weight)**	**Subsequent dose**
Minor (e.g. epistaxis, oral bleeding, menorrhagia)	40 to 50 IU/kg	40 to 50 IU/kg every 8 to 24 hours (or as long as deemed clinically necessary)
Major [b] (e.g. severe or refractory epistaxis, menorrhagia, gastrointestinal bleeding, central nervous system trauma, haemarthrosis, or traumatic haemorrhage)	50 to 80 IU/kg	40 to 60 IU/kg every 8 to 24 hours for approximately 2-3 days (or as long as deemed clinically necessary)

[a] If rFVIII is administered, see rFVIII package insert for reconstitution and administration instructions.
[b] A bleed could be considered major if red blood cell transfusion is either required or potentially indicated or if bleeding occurs in a critical anatomical site (e.g., intracranial or gastrointestinal haemorrhage).

Prevention of bleeding/haemorrhage and treatment in case of elective surgery

Assess FVIII:C levels prior to initiation of any surgical procedure. The recommended minimum target levels are 0.4 IU/mL for minor and oral surgery and 0.8 IU/mL for major surgery.

To ensure pre-operative endogenous FVIII levels of at least 0.4 IU/mL for minor and oral and 0.8 IU/mL for major surgery, a dose of 40-60 IU/kg VEYVONDI may be administered 12-24 hours (pre-operative dose) prior to initiating elective surgery. Within 1 hour prior to surgery, patients should receive a dose of VEYVONDI based on the assessment 3 hours before surgery. The dose depends on VWF and FVIII levels of the patient, the type and severity of the bleeding.

If the FVIII:C levels are not at the recommended target, a dose of VEYVONDI alone should be administered within 1 hour prior to the procedure. If the FVIII:C levels are not at the recommended target levels, rFVIII should be administered in addition to vonicog alfa to raise VWF:RCo and FVIII:C. Please refer to **Table 2** for FVIII:C recommended target levels.

Table 2.
Recommended target peak plasma levels of VWF:RCo and FVIII:C to be achieved prior to surgery for the prevention of excessive bleeding during and after surgery

Type of surgery	VWF:RCo target peak plasma level	FVIII:C target peak plasma level [a]	Calculation of rVWF dose (to be administered within 1 hour prior to surgery) (IU VWF:RCo required)
Minor	0.5-0.6 IU/mL	0.4 – 0.5 IU/mL	Δ[b] VWF:RCo x BW (kg) /IR [c]
Major	1 IU/mL	0.80 – 1 IU/mL	Δ[b] VWF:RCo x BW (kg) /IR [c]

[a] Additional rFVIII may be required to attain the recommended FVIII:C target peak plasma levels. Dosing guidance should be done based on the IR.
[b] Δ = Target peak plasma VWF:RCo – baseline plasma VWF:RCo
[c] IR = Incremental Recovery as measured in the subject. If the IR is not available, assume an IR of 0.02 IU/mL per IU/kg.

During and after surgery
After the initiation of the surgical procedure, the VWF:RCo and FVIII:C plasma levels should be monitored and the intra- and post-operative substitution regimen should be individualized according to the PK results, intensity and duration of the haemostatic challenge, and the institution's standard of care. In general, the frequency of VEYVONDI dosing for post-operative substitution should range from twice a day to every 48 hours. Refer to Table 3 for treatment recommendations for subsequent maintenance doses.

Table 3.
Recommended target trough plasma levels of VWF: RCo and FVIII:C and minimum duration of treatment for subsequent maintenance doses for the prevention of excessive bleeding after surgery

Type of surgery	VWF: RCo target trough plasma level		FVIII:C target trough plasma level		Minimum duration of treatment	Frequency of dosing
	Up to 72 hours post surgery	After 72 hours post surgery	Up to 72 hours post surgery	After 72 hours post surgery		
Minor	≥ 0.30 IU/mL	-	> 0.40 IU/mL	-	48 hours	Every 12-24 hrs / every other day
Major	> 0.50 IU/mL	> 0.30 IU/mL	> 0.50 IU/mL	> 0.40 IU/mL	72 hours	Every 12-24 hrs / every other day

Prophylactic treatment
For initiation of long-term prophylaxis against bleeds in patients with VWD doses of 40 to 60 IU/kg of VEYVONDI administered twice weekly should be considered. Depending on the patient's condition and clinical response, including breakthrough bleeds, higher doses (not exceeding 80 IU/kg) and/or an increased dose frequency (up to three times per week) may be required.

Name and batch number of the medicinal product

It is strongly recommended that every time that VEYVONDI is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.