NovoEight®

250 IU, 500 IU, 1000 IU, 1500 IU, 2000 IU and 3000 IU
powder and solvent for solution for injection

Qualitative and quantitative composition

Turoctocog alfa.
Each vial contains nominally 250, 500, 1000, 1500, 2000 or 3000 IU human coagulation factor VIII (rDNA), turoctocog alfa.

NovoEight® contains approximately 62.5, 125, 250, 375, 500 or 750 IU/ml of human coagulation factor VIII (rDNA), turoctocog alfa after reconstitution.

The potency (IU) is determined using the European Pharmacopoeia chromogenic assay. The specific activity of NovoEight® is approximately 8,300 IU/mg protein.

Turoctocog alfa (human coagulation factor VIII (rDNA)) is a purified protein that has 1,445 amino acids with an approximate molecular mass of 166 kDa. It is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells. It is a third generation factor VIII product prepared without the addition of any human or animal derived protein in the cell culture process, purification or final formulation.

Turoctocog alfa is a B-domain truncated recombinant human coagulation factor VIII (B-domain consists of 21 amino acids of the endogenous type B-domain) without any other modifications in the amino acid sequence.

Excipient with known effect:
0.31 mmol sodium (corresponding to 18 mg sodium chloride) per ml of reconstituted solution.
For the full list of excipients, see *List of excipients*.

Pharmaceutical form

Powder and solvent for solution for injection.

White or slightly yellow powder or friable mass.

Clear and colourless solution for injection.

Clinical particulars

Therapeutic indications

Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).

NovoEight® can be used for all age groups.

Posology and method of administration

Treatment should be initiated under the supervision of a doctor experienced in the treatment of haemophilia.

Posology

The dosage and duration of the substitution therapy depend on the severity of the factor VIII deficiency, on the location and extent of the bleeding and the patient's clinical condition.

The number of units of factor VIII administered is expressed in International Units (IU), which are related to the current WHO standard for factor VIII products. The activity of factor VIII in plasma is expressed either as percentage (relative to normal level human plasma) or in International Units (relative to an International Standard for factor VIII in plasma).

One IU of factor VIII activity is equivalent to that quantity of factor VIII in one ml normal human plasma.

On-demand treatment
The calculation of the required dose of factor VIII is based on the empirical finding that 1 IU factor VIII per kg body weight raises the plasma factor VIII activity by 2 IU/dl. The required dose is determined using the following formula:

Required units (IU) = body weight (kg)× desired factor VIII rise (%) (IU/dl)×0.5 (IU/kg per IU/dl).

The amount to be administered and frequency of administration should always be oriented to the clinical effectiveness in the individual case.

In case of the following haemorrhagic events, the factor VIII activity should not fall below the given plasma activity level (in % of normal or IU/dl) in the corresponding period. The following table can be used to guide dosing in bleeding episodes and surgery:

Table 1 Guide for dosing in bleeding episodes and surgery

Degree of haemorrhage/Type of surgical procedure	FVIII level required (%) (IU/dl)	Frequency of doses (hours)/Duration of therapy (days)
Haemorrhage		
Mild Early haemarthrosis, muscle bleeding or oral bleeding	20–40	Repeat every 12 to 24 hours, at least 1 day, until the bleeding episode as indicated by pain is resolved or healing achieved
Moderate More extensive haemarthrosis, muscle bleeding or haematoma	30–60	Repeat injection every 12–24 hours for 3–4 days or more until pain and acute disability are resolved
Major Life threatening haemorrhages	60–100	Repeat injection every 8 to 24 hours until threat is resolved
Surgery		
Minor surgery Including tooth extraction	30–60	Every 24 hours, at least 1 day, if needed until healing is achieved
Major surgery	80–100 (pre-and postoperative)	Repeat injection every 8–24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a factor VIII activity of 30% to 60% (IU/dl)

Prophylaxis
For long term prophylaxis against bleeding in patients with severe haemophilia A. The usual recommended doses are 20–40 IU of factor VIII per kg body weight every second day or 20–50 IU of factor VIII per kg body weight 3 times weekly. In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

Treatment monitoring
During the course of treatment, appropriate determination of factor VIII levels is advised to guide the dose to be administered and the frequency of repeated injections. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor VIII activity) is indispensable. Individual patients may vary in their response to factor VIII, achieving different levels of *in vivo* recovery and demonstrating different half-lives.

Elderly people
There is no experience in patients >65 years.

Paediatric population
For long term prophylaxis against bleeding in patients below the age of 12, doses of 25–50 IU of factor VIII per kg body weight every second day or 25–60 IU of factor VIII per kg body weight 3 times weekly are recommended. For paediatric patients above the age of 12 the dose recommendations are the same as for adults.

Surgery
There is no experience in major surgery of paediatric patients.

Previously untreated patients
The safety and efficacy in previously untreated patients have not yet been established. No data are available.

Method of administration

Intravenous use.

The recommended injection rate for NovoEight® is 1–2 ml/min. The rate should be determined by the patient's comfort level.

For instructions on reconstitution of the medicinal product before administration, see *Instructions on how to use NovoEight®*.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in *List of excipients*.

Known allergic reaction to hamster protein.

Special warnings and precautions for use

Hypersensitivity
As with any intravenous protein product, allergic type hypersensitivity reactions are possible with NovoEight®. The product contains traces of hamster proteins, which in some patients may cause allergic reactions. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of NovoEight® immediately and contact their physician and/or seek emergency medical treatment. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis.

In case of anaphylactic shock, standard medical treatment for shock should be implemented.

Inhibitors
The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma using the modified assay. The risk of developing inhibitors is correlated to the exposure to factor VIII, the risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days.

In general, all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observation and laboratory test. If the expected factor VIII activity is not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed. In patients with inhibitors, factor VIII therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of haemophilia and factor VIII inhibitors.

It is strongly recommended that every time that NovoEight® 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 medicinal product.

Excipient related considerations
After reconstitution this medicinal product contains 0.31 mmol sodium (corresponding to 18 mg sodium chloride) per ml of reconstituted solution. To be taken into consideration by patients on a controlled sodium diet.

Paediatric population
The listed warnings and precautions apply both to adults and children.

Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with NovoEight®.

Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with NovoEight®. Based on the rare occurrence of haemophilia A in women, experience regarding the use of factor VIII during pregnancy and breast-feeding is not available. Therefore, NovoEight® should only be used during pregnancy and lactation if clearly indicated.

Effects on ability to drive and use machines

NovoEight® has no influence on the ability to drive and use machines.

Undesirable effects

Description of selected adverse reactions
During all clinical studies with NovoEight®, a total of 30 adverse reactions were reported in 19 of 214 patients exposed to NovoEight®. The most frequently reported adverse reactions were injection site reactions and hepatic enzymes increased. Of the 30 adverse reactions, 2 were reported in 1 out of 31 patients below 6 years of age, none in patients from 6 to 18 years of age and 28 were reported in 18 out of 127 adults.

Patients with haemophilia A may develop neutralising antibodies (inhibitors) to factor VIII. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre is contacted.

Tabulated list of adverse reactions
The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).

Frequencies have been evaluated according to the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000); not known (cannot be estimated from the available data).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2 Frequency of adverse drug reactions in clinical trials

System Organ Class	Frequency*	Adverse reaction
Psychiatric disorders	Uncommon	Insomnia
Nervous System Disorders	Uncommon	Headache, dizziness
Cardiac disorders	Uncommon	Sinus tachycardia
Vascular disorders	Uncommon	Hypertension, lymphoedema
Hepatobiliary disorders	Common	Hepatic enzymes increased**
Skin and subcutaneous tissue disorders	Uncommon	Rash
Musculoskeletal and connective tissue disorders	Uncommon	Musculoskeletal stiffness, arthropathy, pain in extremity, musculoskeletal pain
General disorders and administration site conditions	Common	Injection site reactions***
	Uncommon	Fatigue, feeling hot, oedema peripheral, pyrexia
Investigations	Uncommon	Heart rate increased
Injury, poisoning and procedural complications	Uncommon	Contusion

* Calculated based on total number of unique patients in all clinical studies (214).
** Hepatic enzymes increased includes alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltransferase and bilirubin.
*** Injection site reactions include injection site erythema, injection site extravasation and injection site pruritus.

Paediatric population
In clinical studies involving 63 paediatric patients between 0 and 12 years of age and 24 adolescents between 12 and 18 years of age with severe haemophilia A no difference in the safety profile of NovoEight® was observed between paediatric patients and adults.

Overdose

No symptoms of overdose with recombinant coagulation factor VIII have been reported.

Pharmacological properties

Pharmacodynamic properties

Pharmacotherapeutic group: antihemorrhagics, blood coagulation factor VIII.
ATC code: B02BD02

Mechanism of action

Turoctocog alfa (human coagulation factor VIII (rDNA)) is a purified protein that has 1,445 amino acids with an approximate molecular mass of 166 kDa (calculated excluding post-translational modifications). The turoctocog alfa molecule is a polypeptide containing a heavy chain of 87 kDa and a light chain of 79 kDa held together by non-covalent interactions. In endogenous type factor VIII the heavy chain contains varying lengths of B-domain, which in turoctocog alfa is a truncated B-domain with 21 amino acid residues. Six potential sites for tyrosine sulfation have been shown to be sulfated in the turoctocog alfa molecule. The tyrosine sulfation site corresponding to Tyr1680 in the (endogenous full length) factor VIII, which is important for the binding to von Willebrand factor, has been found to be fully sulfated in the turoctocog alfa molecule.

NovoEight® contains human coagulation factor VIII (rDNA), turoctocog alfa, a glycoprotein that has the same structure as human factor VIII when activated, and post-translational modifications that are similar to those of the plasma-derived molecule. When infused into a haemophilia patient, factor VIII binds to endogenous von Willebrand factor in the patient's circulation. The factor VIII/von Willebrand factor complex consists of two molecules (factor VIII and von Willebrand factor) with different physiological functions. Activated factor VIII acts as a co-factor for activated factor IX, accelerating the conversion of factor X to activated factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed. Haemophilia is a sex-linked hereditary disorder of blood coagulation due to decreased levels of factor VIII:C and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma levels of factor VIII are increased, thereby enabling a temporary correction of the factor deficiency and correction of bleeding tendencies.

Pharmacokinetic properties

All pharmacokinetic studies with NovoEight® were conducted in previously treated patients with severe haemophilia A (factor VIII ≤1%). The analysis of plasma samples was conducted using both the one-stage clotting assay and the chromogenic assay.

The single dose pharmacokinetic parameters of NovoEight® are listed in Table 3 for the one stage clotting assay and Table 4 for the chromogenic assay.

Table 3 Single-dose pharmacokinetics of NovoEight® in patients with severe haemophilia A (FVIII ≤1%), clotting assay

Parameter	0 – <6 years	6 – <12 years	≥12 years
	n=14	n=14	n=33
	Mean (SD)	Mean (SD)	Mean (SD)
Incremental recovery (IU/ml)/(IU/kg)	0.018 (0.007)	0.020 (0.004)	0.022 (0.004)
AUC ((IU*h)/ml)	9.92 (4.11)	11.09 (3.74)	15.26 (5.77)
CL (ml/h/kg)	6.21 (3.66)	5.02 (1.68)	3.63 (1.09)
$t_{½}$ (h)	7.65 (1.84)	8.02 (1.89)	11.00 (4.65)
V_{ss} (ml/kg)	56.68 (26.43)	46.82 (10.63)	47.40 (9.21)
C_{max} (IU/ml)	1.00 (0.58)	1.07 (0.35)	1.226 (0.41)
Mean residence time (h)	9.63 (2.50)	9.91 (2.57)	14.19 (5.08)

Table 4 Single-dose pharmacokinetics of NovoEight® in patients with severe haemophilia A (FVIII ≤1%), chromogenic assay

Parameter	0 – <6 years	6 – <12 years	≥12 years
	n=14	n=14	n=33
	Mean (SD)	Mean (SD)	Mean (SD)
Incremental recovery (IU/ml)/(IU/kg)	0.022 (0.006)	0.025 (0.006)	0.029 (0.006)
AUC ((IU*h)/ml)	12.23 (4.36)	14.37 (3.48)	19.63 (7.73)
CL (ml/h/kg)	4.59 (1.73)	3.70 (1.00)	2.86 (0.94)
$t_{½}$ (h)	9.99 (1.71)	9.42 (1.52)	11.22 (6.86)
V_{ss} (ml/kg)	55.46 (23.53)	41.23 (6.00)	38.18 (10.24)
C_{max} (IU/ml)	1.12 (0.31)	1.25 (0.27)	1.63 (0.50)
Mean residence time (h)	12.06 (1.90)	11.61 (2.32)	14.54 (5.77)

The pharmacokinetic parameters were comparable between paediatric patients below 6 years of age and the paediatric patients from 6 to below 12 years of age. Some variation was observed in the pharmacokinetic parameters of NovoEight® between paediatric and adult patients. The higher CL and the shorter t½ seen in paediatric patients compared to adult patients with haemophilia A may be due in part to the known higher plasma volume per kilogram body weight in younger patients.

A multi-centre, randomised and blinded field study of simulated post-injection plasma samples has been conducted to evaluate activity and assay performance and variability of NovoEight® in spiked plasma from patients with haemophilia A at different clinical laboratories with the methodology and reagents routinely used in the laboratories. A total of 36 laboratories participated in the study; 33 laboratories used the one-stage clotting assay; 5 used the chromogenic assay, and 2 laboratories used both assays. Comparable and consistent estimates of target value were observed for NovoEight® among the participating laboratories.

Preclinical safety data

Non-clinical data reveal no special concern for humans based on conventional studies of safety pharmacology and repeated dose toxicity.

Pharmaceutical Particulars

List of excipients

Powder:
Sodium chloride, L-histidine, sucrose, polysorbate 80, L-methionine, calcium chloride dihydrate, sodium hydroxide and hydrochloric acid.

Solvent:
Sodium chloride and water for injections.

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf life

During the shelf life, the product may be kept at room temperature ≤30°C for a single period not exceeding 6 months. Once the product has been taken out of the refrigerator the product must not be returned to the refrigerator. Please record the beginning of storage at room temperature on the product carton.

Do not use this medicine after the expiry date which is stated after expiry on the carton and on the vial and the prefilled syringe labels. The expiry date refers to the last day of that month.

Keep the vial in the outer carton in order to protect it from light.

After reconstitution:
Chemical and physical in-use stability have been demonstrated for 24 hours stored at 2°C – 8°C and 4 hours stored at ≤30°C. From a microbiological point of view, the medicinal product should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the users and would normally not be longer than 4 hours stored at ≤30°C or 24 hours at 2°C – 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Any unused product stored at room temperature for more than 4 hours should be discarded.

Special precautions for storage

Store in refrigerator (2°C – 8°C). Do not freeze.

For storage at room temperature and storage conditions after reconstitution of the medicinal product, see *Shelf life*.

Nature and contents of container

Each pack of NovoEight® 250–3000 IU powder and solvent for solution for injection contains:
– 1 glass vial (type I) with powder and chlorobutyl rubber stopper
– 1 sterile vial adaptor for reconstitution
– 1 prefilled syringe of 4 ml solvent with backstop (polypropylene), a rubber plunger (bromobutyl) and a tipcap with a stopper (bromobutyl)
– 1 plunger rod (polypropylene)

Marketing authorisation holder

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

NovoEight® is a trademark owned by Novo Nordisk A/S, Denmark.

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powder and solvent for solution for injection

8-9063-00-001-1

NovoEight®
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Instructions on how to use NovoEight®

READ THESE INSTRUCTIONS CAREFULLY BEFORE USING NOVOEIGHT®.
NovoEight® is supplied as a powder. Before injection (administration) it must be reconstituted with the solvent supplied in the syringe. The solvent is a sodium chloride buffer. The reconstituted NovoEight® must be injected into your vein (intravenous injection). The equipment in this package is designed to reconstitute and inject NovoEight®.
You will also need an infusion set (tubing and butterfly needle), sterile alcohol swabs, gauze pads and plasters. These devices are not included in the NovoEight® package.

Do not use the equipment without proper training from your doctor or nurse.
Always wash your hands and ensure that the area around you is clean.

When you prepare and inject medication directly into the veins, it is important to **use a clean and germ free (aseptic) technique.** Improper technique can 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 is expired. Use a new package instead. The expiry date is printed after expiry on the outer carton, on the vial, on the vial adapter, and on the prefilled syringe.

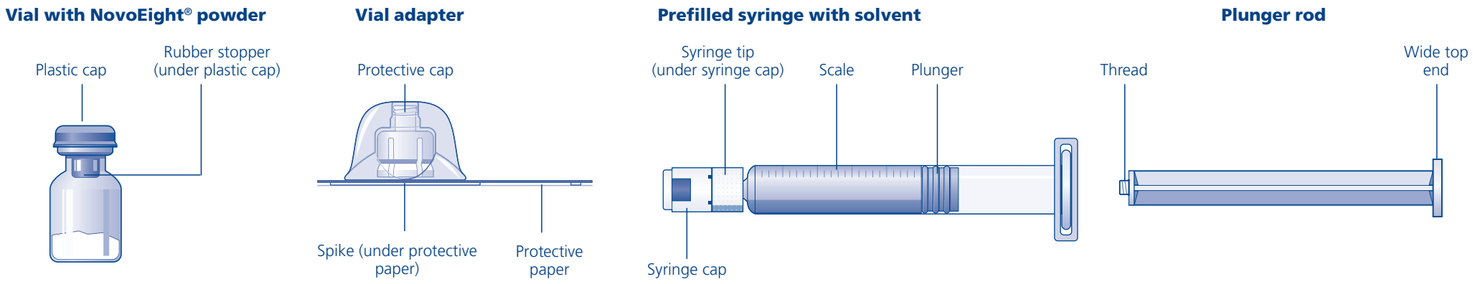
Do not use the equipment if you suspect it is contaminated. Use a new package instead.

Do not dispose of any of the items until after you have injected the reconstituted solution.
The equipment is for single use only.

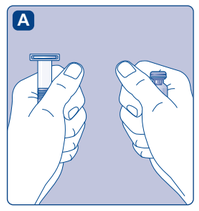
Contents

The package contains:
- 1 vial with NovoEight® powder
- 1 vial adapter
- 1 prefilled syringe with solvent
- 1 plunger rod (placed under the syringe)

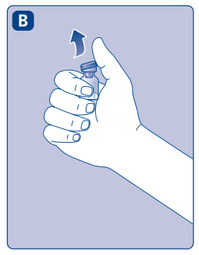
Overview



1. Prepare the vial and the syringe

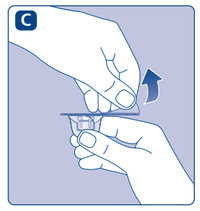


- **Take out the number of NovoEight® packages you need.**
- **Check the expiry date.**
- **Check the name, strength and colour** of the package, to make sure it contains the correct product.
- **Wash your hands** and dry them properly using a clean towel or air dry.
- Take the vial, the vial adapter and the prefilled syringe out of the carton. **Leave the plunger rod untouched in the carton.**
- **Bring the vial and the prefilled 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 heat** the vial and prefilled 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 before use to ensure that it is as germ free as possible.
- **Do not touch the rubber stopper with your fingers as this can transfer germs.**

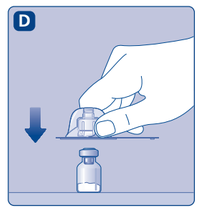
2. Attach the vial adapter



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

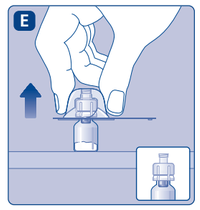
If the protective paper is not fully sealed or if it is broken, do not use the vial adapter.

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 can be transferred.



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

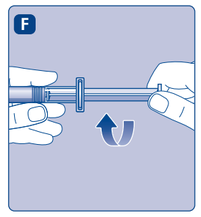
Once attached, do not remove the vial adapter from the vial.



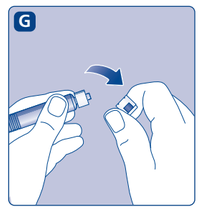
- Lightly **squeeze the protective cap** with your thumb and index finger as shown.

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

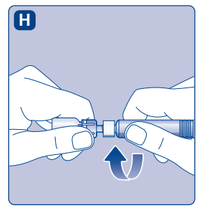


- Grasp the plunger rod by the wide top end and take it out of the carton. **Do not touch the sides or the thread of the plunger rod.** If you touch the sides or the thread, germs from your fingers can be transferred.
- **Immediately** connect the plunger rod to the syringe by turning it clockwise into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



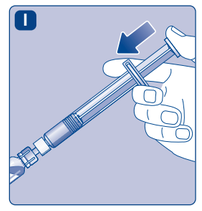
- **Remove the syringe cap** from the prefilled syringe by bending it down until the perforation breaks.
- **Do not touch the syringe tip under the syringe cap.** If you touch the syringe tip, germs from your fingers can be transferred.

If the syringe cap is loose or missing, do not use the prefilled syringe.

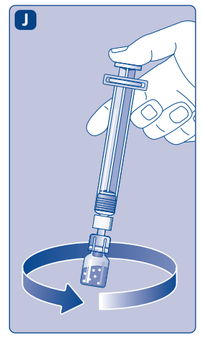


- **Screw the prefilled syringe securely** onto the vial adapter until resistance is felt.

4. Reconstitute the powder with the solvent



- **Hold the prefilled 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 to slightly opalescent (slightly unclear). **If you notice visible particles or discolouration, do not use it.** Use a new package instead.

NovoEight® is recommended to be used immediately after it has been reconstituted. This is because if left, the medicine may no longer be sterile and could cause infections.

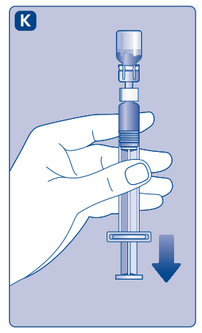
If you cannot use the reconstituted NovoEight® solution immediately, it should be used within 4 hours when stored below 30°C and within 24 hours when stored at 2°C – 8°C. Store the reconstituted product in the vial, still with the vial adapter and the syringe attached.

Do not freeze reconstituted NovoEight® solution or store it in syringes.

Do not store the solution without your doctor's advice.

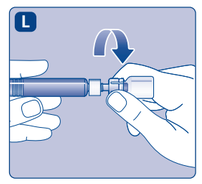
Keep reconstituted NovoEight® solution out of direct light.

If your dose requires more than one vial, repeat steps **A** to **J** with additional vials, vial adapters and prefilled 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 slightly downwards** to draw the reconstituted solution into the syringe.
- **In case you only need part of the entire vial, use the scale on the syringe to see how much reconstituted solution you withdraw, as instructed by your doctor or nurse.**

If, at any point, there is too much 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 can be transferred.

5. Inject the reconstituted solution

NovoEight® is now ready to inject into your vein.
- Inject the reconstituted solution as instructed by your doctor or nurse.
- Inject slowly over 2 to 5 minutes.
- Do not mix NovoEight® with any other intravenous infusions or medications.

Injecting the solution via central venous catheter or permanent port:
- Use a clean and germ free (aseptic) technique. Ask your doctor or nurse for specific instructions.
- If the line needs to be flushed before or after NovoEight® injection, use sodium chloride 9 mg/ml (0.9%) solution for injection.

Disposal

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

Do not throw it out with the ordinary household waste.

Do not disassemble the equipment before disposal.
Do not reuse the equipment.