ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Nuwiq 250 IU powder and solvent for solution for injection
Nuwiq 500 IU powder and solvent for solution for injection
Nuwiq 1000 IU powder and solvent for solution for injection
Nuwiq 1500 IU powder and solvent for solution for injection
Nuwiq 2000 IU powder and solvent for solution for injection
Nuwiq 2500 IU powder and solvent for solution for injection
Nuwiq 3000 IU powder and solvent for solution for injection
Nuwiq 4000 IU powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nuwiq 250 IU powder and solvent for solution for injection

Each vial contains nominally 250 IU human coagulation factor VIII (rDNA), simoctocog alfa. Nuwiq 250 IU contains approximately 100 IU/mL of human coagulation factor VIII (rDNA), simoctocog alfa after reconstitution.

Nuwiq 500 IU powder and solvent for solution for injection

Each vial contains nominally 500 IU human coagulation factor VIII (rDNA), simoctocog alfa. Nuwiq 500 IU contains approximately 200 IU/mL of human coagulation factor VIII (rDNA), simoctocog alfa after reconstitution.

Nuwiq 1000 IU powder and solvent for solution for injection

Each vial contains nominally 1000 IU human coagulation factor VIII (rDNA), simoctocog alfa. Nuwiq 1000 IU contains approximately 400 IU/mL of human coagulation factor VIII (rDNA), simoctocog alfa after reconstitution.

Nuwiq 1500 IU powder and solvent for solution for injection

Each vial contains nominally 1500 IU human coagulation factor VIII (rDNA), simoctocog alfa. Nuwiq 1500 IU contains approximately 600 IU/mL of human coagulation factor VIII (rDNA), simoctocog alfa after reconstitution.

Nuwiq 2000 IU powder and solvent for solution for injection

Each vial contains nominally 2000 IU human coagulation factor VIII (rDNA), simoctocog alfa. Nuwiq 2000 IU contains approximately 800 IU/mL of human coagulation factor VIII (rDNA), simoctocog alfa after reconstitution.

Nuwiq 2500 IU powder and solvent for solution for injection

Each vial contains nominally 2500 IU human coagulation factor VIII (rDNA), simoctocog alfa. Nuwiq 2500 IU contains approximately 1000 IU/mL of human coagulation factor VIII (rDNA), simoctocog alfa after reconstitution.

Nuwiq 3000 IU powder and solvent for solution for injection

Each vial contains nominally 3000 IU human coagulation factor VIII (rDNA), simoctocog alfa. Nuwiq 3000 IU contains approximately 1200 IU/mL of human coagulation factor VIII (rDNA), simoctocog alfa after reconstitution.

Nuwiq 4000 IU powder and solvent for solution for injection

Each vial contains nominally 4000 IU human coagulation factor VIII (rDNA), simoctocog alfa. Nuwiq 4000 IU contains approximately 1600 IU/mL of human coagulation factor VIII (rDNA), simoctocog alfa after reconstitution.

The potency (IU) is determined using the European Pharmacopoeia chromogenic assay. The specific activity of Nuwiq is approximately 9500 IU/mg protein.

Simoctocog alfa (human coagulation factor VIII (rDNA)) is a purified protein that has 1440 amino acids. The amino acid sequence is comparable to the 90 + 80 kDa form of human plasma factor VIII (i.e. B-domain deleted). Nuwiq is produced by recombinant DNA technology in genetically modified human embryonic kidney (HEK) 293F cells. No animal or human derived materials are added during the manufacturing process or to the final medicinal product.

Excipient with known effect

One mL of reconstituted solution contains 7.35 mg sodium (18.4 mg sodium per vial).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Powder: white to off-white friable powder.

Solvent: a clear, colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).
Nuwiq can be used for all age groups.

4.2 Posology and method of administration

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

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 infusions. Individual patients may vary in their response to factor VIII, demonstrating different half-lives and recoveries. Dose based on bodyweight may require adjustment in underweight or overweight patients. 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.

When using an *in vitro* thromboplastin time (aPTT)-based one stage clotting assay for determining factor VIII activity in patients' blood samples, plasma factor VIII activity results can be significantly affected by both the type of aPTT reagent and the reference standard used in the assay. Also there can be significant discrepancies between assay results obtained by aPTT-based one stage clotting assay and the chromogenic assay according to Ph. Eur. This is of importance particularly when changing the laboratory and/or reagents used in the assay.

Posology

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

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

One International Unit (IU) of factor VIII activity is equivalent to the quantity of factor VIII in one mL of normal human plasma.

On-demand treatment

The calculation of the required dose of factor VIII is based on the empirical finding that 1 International Unit (IU) factor VIII per kg body weight raises the plasma factor VIII activity by approximately 2% of normal activity or 2 IU/dL. The required dose is determined using the following formula:

Required units = body weight (kg) x desired factor VIII rise (%) (IU/dL) x 0.5 (IU/kg per IU/dL)

$$\text{Expected factor VIII rise (\% of normal)} = \frac{2 \times \text{administered IU}}{\text{body weight (kg)}}$$

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

In the case of the following haemorrhagic events, 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.

Degree of haemorrhage/ Type of surgical procedure	**Factor VIII level required (%) (IU/dL)**	**Frequency of doses (hours)/ Duration of therapy (days)**
Haemorrhage		
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 is achieved.
More extensive haemarthrosis, muscle bleeding or haematoma	30–60	Repeat infusion every 12 to 24 hours for 3 to 4 days or more until pain and acute disability are resolved.
Life threatening haemorrhages	60–100	Repeat infusion every 8 to 24 hours until threat is resolved.
Surgery		
Minor surgery including tooth extraction	30–60	Every 24 hours, at least 1 day, until healing is achieved.
Major surgery	80–100 (pre- and postoperative)	Repeat infusion 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 doses are 20 to 40 IU of factor VIII per kg body weight at intervals of 2 to 3 days. The regimen may be adjusted based on patient response.

In some cases, especially in younger patients, shorter dose intervals or higher doses may be necessary.

Paediatric population

The posology is the same in adults and children and adolescents, however, shorter dose intervals or higher doses may be necessary for children and adolescents. Currently available data are described in sections 4.8, 5.1 and 5.2.

Method of administration

Nuwiq is for intravenous use.
It is recommended that not more than 4 mL per minute be administered.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity

As with any intravenous protein product, allergic type hypersensitivity reactions are possible. Nuwiq contains traces of human host cell proteins other than factor VIII. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the medicinal product immediately and contact their physician. 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 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 severity of the disease as well as the exposure to factor VIII, this risk being highest within the first 50 exposure days but continues throughout life although the risk is uncommon.

Cases of recurrent inhibitor (low titre) have been observed after switching from one factor VIII product to another in previously treated patients with more than 100 exposure days who have a previous history of inhibitor development. Therefore, it is recommended to monitor all patients carefully for inhibitor occurrence following any product switch.

The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with low titre inhibitors which are transiently present or remain consistently low titre posing less of a risk of insufficient clinical response than high titre inhibitors.

In general, all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed. In patients with high levels of inhibitor, 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.

Cardiovascular events

In patients with existing cardiovascular risk factors, substitution therapy with FVIII may increase the cardiovascular risk.

Catheter-related complications

If a central venous access device (CVAD) is required, risk of CVAD-related complications including local infections, bacteraemia and catheter site thrombosis should be considered.

Paediatric population

The listed warnings and precautions apply both to adults and children and adolescents.

Excipient related considerations (sodium content)

This medicinal product contains 18.4 mg sodium per vial, equivalent to 0.92 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with Nuwiq.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with factor VIII.
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, factor VIII should be used during pregnancy and breast-feeding only if clearly indicated. There are no fertility data available.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Hypersensitivity or allergic reactions (which may include angiooedema, burning and stinging at the infusion site, chills, flushing, headache, hives, hypotension, lethargy, nausea, rash, restlessness, tachycardia, tightness of the chest, tingling, urticaria, including generalised urticaria, vomiting, wheezing) have rarely been observed with FVIII preparations and may in some cases progress to severe anaphylaxis (including shock).

Development of neutralising antibodies (inhibitors) may occur in patients with haemophilia A treated with factor VIII, including with Nuwiq. 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 be contacted.

Tabulated list of adverse reactions

Table 1 presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level). Frequencies are based on reports from clinical trials with a total of 355 unique subjects with severe haemophilia A, of which 247 were previously treated patients (PTPs) and 108 were previously untreated patients (PUPs).

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 1. Frequency of adverse reactions in clinical studies

MedDRA Standard System Organ Class	Adverse reactions	Frequency
Blood and lymphatic system disorders	Anaemia Factor VIII inhibition Haemorrhagic anaemia	Uncommon* Uncommon (PTPs) [#] Very common (PUPs)[#] Uncommon*
Immune system disorders	Hypersensitivity	Common*
Nervous system disorders	Dizziness Headache Paraesthesia	Uncommon* Uncommon* Uncommon*
Ear and labyrinth disorders	Vertigo	Uncommon*
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Uncommon*
Gastrointestinal disorders	Dry mouth	Uncommon*
Musculoskeletal and connective tissue disorders	Back pain	Uncommon*
General disorders and administration site conditions	Pyrexia Chest pain Injection site inflammation Injection site pain Malaise	Common* Uncommon* Uncommon* Uncommon* Uncommon*
Investigations	Non-neutralising antibody positive (in PTPs)	Uncommon*

* Calculated as patients with adverse reactions per total number of 355 study patients, of which 247 previously treated patients (PTPs) and 108 previously untreated patients (PUPs).

[#] Frequency is based on studies with all FVIII products which included patients with severe haemophilia A. PTPs = previously-treated patients, PUPs = previously-untreated patients

Description of selected adverse reactions

A non-neutralizing anti-factor VIII antibody was detected in one adult patient (see Table 1). The sample was tested by the central laboratory at eight dilutions. The result was positive only at dilution factor 1 and the antibody titre was very low. Inhibitory activity, as measured by the modified Bethesda assay, was not detected in this patient. Clinical efficacy and *in vivo* recovery of Nuwiq was not affected in this patient.

Paediatric population

Frequency, type and severity of adverse reactions in children and adolescents are assumed to be the same as in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No cases of overdose have been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

The factor VIII/von Willebrand factor complex consists of two molecules (factor VIII and von Willebrand factor) with different physiological functions. When infused into a haemophiliac patient, factor VIII binds to von Willebrand factor in the patient's circulation. Activated factor VIII acts as a cofactor 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 A 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 results of accidental or surgical trauma. By replacement therapy the plasma levels of factor VIII are increased, thereby temporarily enabling a correction of the factor VIII deficiency and correction of the bleeding tendencies.

Adult and adolescent population 12 - 65 years of age

Prophylaxis
In a clinical study in 32 adult patients with severe haemophilia A, the median consumption of Nuwiq for prophylaxis was 468.7 IU/kg/month.

Treatment of bleeding
The median dose to treat break-through bleeding episodes was 33.0 IU/kg in these patients who were on prophylaxis. In another clinical study, 22 adult patients were treated on demand. In total 986 bleeding episodes were treated with a median dose of 30.9 IU/kg. In general, minor bleeds required slightly lower, and more severe bleeds required up to three-fold higher median doses.

Individualised prophylaxis
Individualised PK-based prophylaxis was evaluated in 66 adult PTPs with severe haemophilia A. Following a 1-3 month standard prophylaxis phase (every other day or 3 times weekly dosing), 44 (67%) patients were switched to a dosing regimen based on their PK assessment, and 40 completed the 6 months of prophylaxis according to the assigned dosing and treatment scheme. Of these patients, 34 (85%) were treated twice weekly or less. 33 (82.5%) patients did not experience any bleeds and 36 (90.0%) patients had no spontaneous bleeds. The mean ± SD annualised bleeding rate was 1.2 ± 3.9 and the mean ± SD dose were 52.2 ± 12.2 IU/kg per injection and 99.7 ± 25.6 IU/kg per week.

Of note, annualised bleeding rate (ABR) is not comparable between different factor concentrates and between different clinical studies.

Paediatric population

Data were obtained in 29 previously treated children between 2 and 5 years of age, 31 children between 6 and 12 years of age and one adolescent of 14 years. The median dose per prophylactic infusion was 37.8 IU/kg. Twenty patients used median doses of more than 45 IU/kg. The median consumption of Nuwiq for prophylaxis per month was 521.9 IU/kg. A higher median dose of Nuwiq was required to treat bleedings in children (43.9 IU/kg) than in adults (33.0 IU/kg), and a higher median dose was required to treat moderate to major than minor bleedings (78.2 IU/kg vs. 41.7 IU/kg). Younger children in general required higher median doses (6-12 years: 43.9 IU/kg; 2-5 years: 52.6 IU/kg). These data were corroborated by a long-term follow-up of 49 of these children who were treated for an additional median period of approximately 30 months (range from 9.5 to 52 months); during this period 45% of children had no spontaneous bleeds.

Data from 108 previously untreated patients with severe haemophilia A (<1% FVIII:C) were obtained in a prospective open-label clinical study. In the majority of patients prophylactic treatment was initiated after the occurrence of the first bleeding episode requiring treatment.

5.2 Pharmacokinetic properties

Adult population

Table 2. PK parameters for Nuwiq (Dose: 50 IU/kg) in adult previously treated patients (age 18-65 years) with severe haemophilia A (n = 20)

PK parameter	Chromogenic assay	
	Mean ± SD	**Median (range)**
AUC (hr*IU/mL)	22.6 ± 8.0	22.3 (8.4 – 38.1)
$T_{1/2}$ (hr)	14.7 ± 10.4	12.5 (5.4 – 55.6)
IVR (%/IU/kg)	2.5 ± 0.4	2.5 (1.7 – 3.2)
CL (mL/hr/kg)	3.0 ± 1.2	2.7 (1.5-6.4)

AUC = Area under the curve (FVIII:C), $T_{1/2}$ = Terminal half-life,
IVR = Incremental *in vivo* recovery, CL = Clearance, SD = Standard deviation

Table 3. PK parameters for Nuwiq (Dose: 50 IU/kg) in previously treated children aged 6 to 12 years with severe haemophilia A (n = 12)

PK parameter	Chromogenic assay	
	Mean ± SD	**Median (range)**
AUC (hr*IU/mL)	13.2 ± 3.4	12.8 (7.8 – 19.1)
$T_{1/2}$ (hr)	10.0 ± 1.9	9.9 (7.6 – 14.1)
IVR (%/IU/kg)	1.9 ± 0.4	1.9 (1.2 – 2.6)
CL (mL/hr/kg)	4.3 ± 1.2	4.2 (2.8 - 6.9)

AUC = Area under the curve (FVIII:C), $T_{1/2}$ = Terminal half-life,
IVR = Incremental *in vivo* recovery, CL = Clearance, SD = Standard deviation

Table 4. PK parameters for Nuwiq (Dose: 50 IU/kg) in previously treated children aged 2 to 5 years with severe haemophilia A (n = 13)

PK parameter	Chromogenic assay	
	Mean ± SD	**Median (range)**
AUC (hr*IU/mL)	11.7 ± 5.3	10.5 (4.9 – 23.8)
$T_{1/2}$ (hr)	9.5 ± 3.3	8.2 (4.3 – 17.3)
IVR (%/IU/kg)	1.9 ± 0.3	1.8 (1.5 – 2.4)

PK parameter	Chromogenic assay	
	Mean ± SD	**Median (range)**
CL (mL/hr/kg)	5.4 ± 2.4	5.1 (2.3 – 10.9)

AUC = Area under the curve (FVIII:C), $T_{1/2}$ = Terminal half-life,
IVR = Incremental *in vivo* recovery, CL = Clearance, SD = Standard deviation

Paediatric population

As known from the literature, recovery and half-life was lower in young children than in adults and clearance higher, which may be due in part to the known higher plasma volume per kilogram body weight in younger patients.

Weight adjusted subgroups

Table 5. Weight-adjusted PK parameters for Nuwiq (Dose: 50 IU/kg) in adult previously treated patients (age 18-65 years) with severe haemophilia A (n = 20)

PK parameter	All (n=20)	Normal weight (n=14)	Pre-adipose (n=4)	Adipose (n=2)
	Chromogenic assay Mean ± SD			
AUC (hr*IU/mL)	22.6 ± 8.0	20.4 ± 6.9	24.9 ± 8.9	33.5 ± 6.5
$T_{1/2}$ (hr)	14.7 ± 10.4	14.7 ± 12.1	13.4 ± 5.9	17.2 ± 4.8
IVR (%/IU/kg)	2.5 ± 0.4	2.4 ± 0.4	2.7 ± 0.4	2.8 ± 0.3
CL (mL/hr/kg)	3.0 ± 1.2	3.2 ± 1.3	2.6 ± 1.0	1.8 ± 0.4
	Chromogenic assay Median (range)			
AUC (hr*IU/mL)	22.3 (8.4 – 38.1)	21.2 (8.4 – 32.6)	23.3 (17.4 – 35.5)	33.5 (28.9 – 38.1)
$T_{1/2}$ (hr)	12.5 (5.4 – 55.6)	12.3 (5.4 – 55.6)	11.2 (9.3 – 22.0)	17.2 (13.8 – 20.6)
IVR (%/IU/kg)	2.5 (1.7 – 3.2)	2.4 (1.7 – 3.1)	2.8 (2.3 – 3.2)	2.8 (2.6 – 3.0)
CL (mL/hr/kg)	2.7 (1.5 – 6.4)	2.8 (1.7 – 6.4)	2.5 (1.6 – 3.7)	1.8 (1.5 – 2.0)

Normal weight: BMI 18.5-25 kg/m^2, Pre-adipose: BMI 25-30 kg/m^2, Adipose: BMI > 30 kg/m^2, SD = Standard deviation

5.3 Preclinical safety data

In pre-clinical studies, Nuwiq was used to safely and effectively restore haemostasis in dogs with haemophilia. Toxicology studies showed that local intravenous administration and systemic exposure were well tolerated in laboratory animals (rats and cynomolgus monkeys).

Specific studies with long-term repeated administration such as reproduction toxicity, chronic toxicity, and carcinogenicity were not performed with Nuwiq due to the immune response to heterologous proteins in all non-human mammalian species.

No studies were performed on the mutagenic potential of Nuwiq.
Ex vivo evaluations using a commercial assay kit to quantify T cell response to protein therapeutics indicate a low risk of immunogenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Sucrose
Sodium chloride
Calcium chloride dihydrate
Arginine hydrochloride

Sodium citrate dihydrate
Poloxamer 188

Solvent

Water for injections

6.2 Incompatibilities

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

Only the provided injection sets should be used because treatment failure can occur as a consequence of human coagulation factor VIII adsorption to the internal surfaces of some injection equipment.

6.3 Shelf life

Unopened vial

2 years

During the shelf-life, the product may be kept at room temperature (up to 25 °C) for a single period not exceeding 1 month. Once the medicinal product has been taken out of the refrigerator, it must not be returned to the refrigerator. Please record the beginning of storage at room temperature on the product carton.

After reconstitution

After reconstitution, chemical and physical in-use stability has been demonstrated for 24 hours when stored at room temperature.

From a microbiological point of view, the 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 user.
Keep the reconstituted solution at room temperature. Do not refrigerate after reconstitution.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Store vial in the original package in order to protect from light.

For storage at room temperature and storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Each pack contains:
- 1 powder vial with 250, 500, 1000, 1500, 2000, 2500, 3000 or 4000 IU simoctocog alfa in a type 1 glass vial, closed with coated bromobutyl stopper and sealed with aluminium flip-off cap
- Solvent: 1 borosilicate pre-filled glass syringe containing 2.5 mL water for injections
- 1 sterile vial adapter for reconstitution with 1 butterfly needle and 2 alcohol swabs

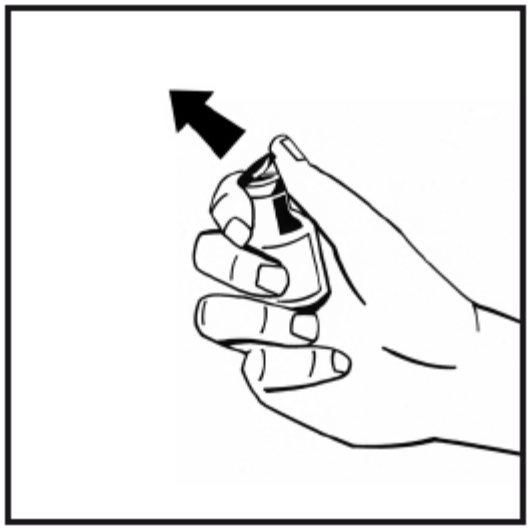
6.6 Special precautions for disposal and other handling

The powder should only be reconstituted with the supplied solvent (2.5 mL water for injections) using the supplied injection set. The vial should be gently rotated until all powder is dissolved. After reconstitution, the solution should be drawn back into the syringe.

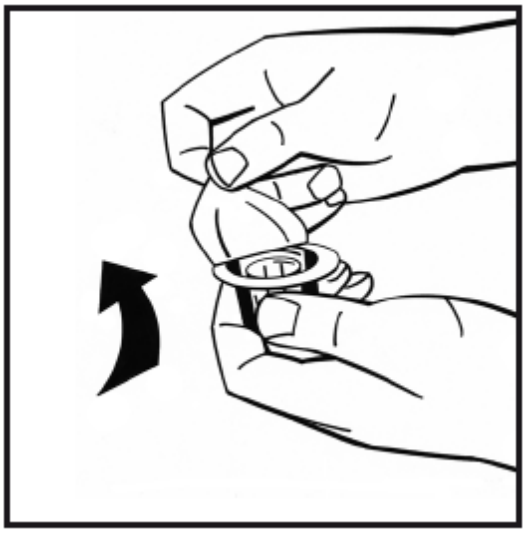
The reconstituted medicinal product should be inspected visually for particulate matter and discoloration prior to administration. The reconstituted medicinal product is a clear, colourless solution, free from foreign particles and has a pH of 6.5 to 7.5. Do not use solutions that are cloudy or have deposits.

Instructions for preparation and administration

1. Allow the solvent syringe (water for injections) and the powder in the closed vial to reach 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 pre-filled syringe. This temperature should be maintained during reconstitution.
2. Remove the plastic flip-off cap from the powder vial to expose the central portions of the rubber stopper. Do not remove the gray stopper or metal ring around the top of the vial.

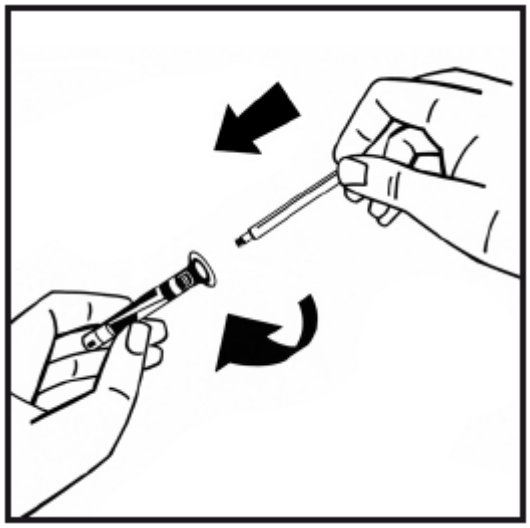


3. Wipe the top of the vial with an alcohol swab. Allow the alcohol to dry.
4. Peel back the paper cover from the vial adapter package. Do not remove the adapter from the package.

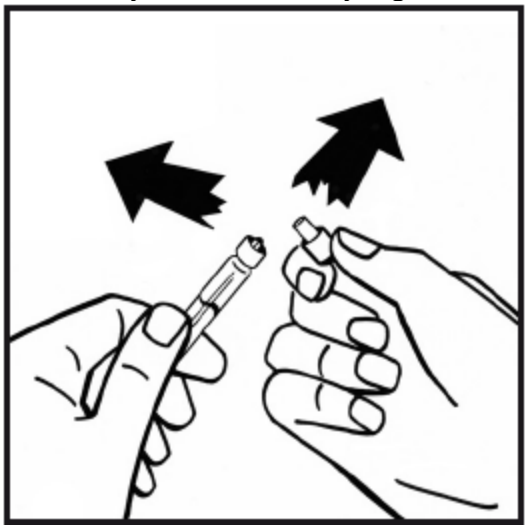


5. Place the powder vial on an even surface and hold it. Take the adapter package and place the vial adapter over the centre of the rubber stopper of the powder vial. Press down firmly the adapter package until the adapter spike penetrates the rubber stopper. The adapter snaps to the vial when done.

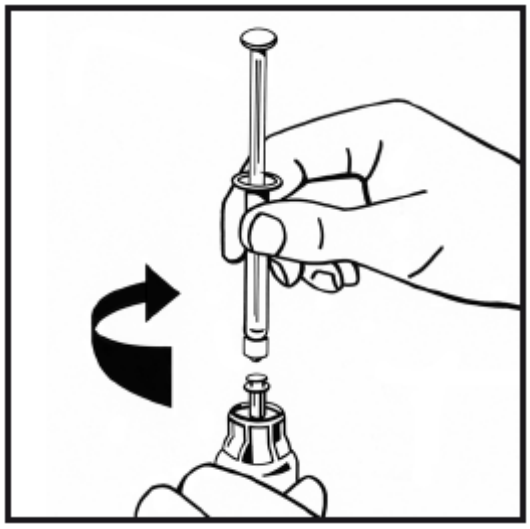
6. Peel back the paper cover from the pre-filled syringe package. Hold the plunger rod at the end and do not touch the shaft. Attach the threaded end of the plunger rod to the solvent syringe plunger. Turn the plunger rod clockwise until a slight resistance is felt.



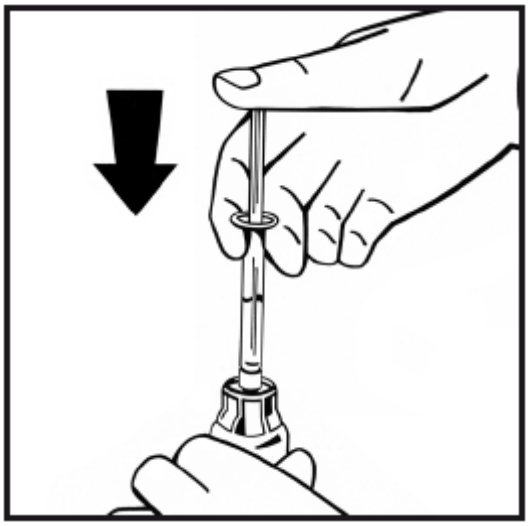
7. Break off the tamper-proof plastic tip from the solvent syringe by snapping the perforation of the cap. Do not touch the inside of the cap or the syringe tip. In case the solution is not used immediately close the filled syringe with the tamper-proof plastic tip for storage.



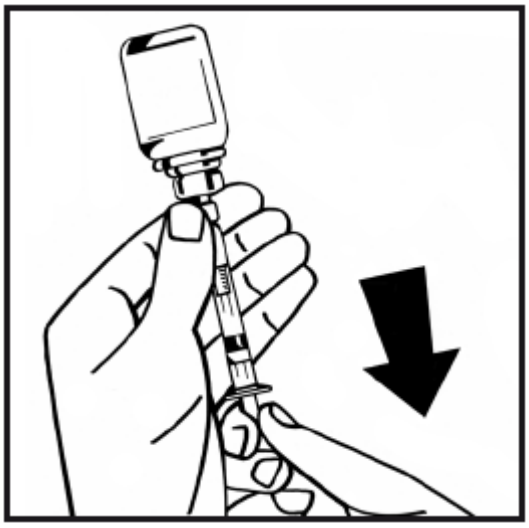
8. Remove the adapter packaging and discard.
9. Firmly connect the solvent syringe to the vial adapter by turning clockwise until resistance is felt.



10. Slowly inject all solvent into the powder vial by pressing down the plunger rod.



11. Without removing the syringe, gently move or swirl the vial in circles a few times to dissolve the powder. Do not shake. Wait until all the powder dissolves completely.
12. Visually inspect the final solution for particles before administration. The solution should be clear and colourless, practically free from visible particles. Do not use solutions that are cloudy or have deposits.
13. Turn the vial attached to the syringe upside down, and slowly draw the final solution into the syringe. Make sure that the entire content of the vial is transferred to the syringe.



14. Detach the filled syringe from the vial adapter by turning counter clockwise and discard the empty vial.

15. The solution is now prepared for immediate use. Do not refrigerate.
16. Clean the chosen injection site with one of the provided alcohol swabs.
17. Attach the provided infusion set to the syringe.
    Insert the needle of the infusion set into the chosen vein. If you have used a tourniquet to make the vein easier to see, this tourniquet should be released before you start injecting the solution. No blood must flow into the syringe due to the risk of formation of fibrin clots.
18. Inject the solution into the vein at a slow speed, not faster than 4 mL per minute.

If you use more than one vial of powder for one treatment, you may use the same injection needle again. The vial adapter and the syringe are for single use only.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Octapharma AB
Lars Forssells gata 23
112 75 Stockholm
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/936/001
EU/1/14/936/002
EU/1/14/936/003
EU/1/14/936/004
EU/1/14/936/005
EU/1/14/936/006
EU/1/14/936/007
EU/1/14/936/008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 July 2014
Date of latest renewal: 26 April 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)
Octapharma AB
Lars Forssells gata 23
Stockholm
11275
Sweden

Name and address of the manufacturer(s) responsible for batch release
Octapharma AB
Lars Forssells gata 23
Stockholm
11275
Sweden

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The marketing authorization holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nuwiq 250 IU powder and solvent for solution for injection
simoctocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 powder vial contains 250 IU simoctocog alfa (100 IU/mL after reconstitution).

3. LIST OF EXCIPIENTS

Excipients: Sucrose, sodium chloride, calcium chloride dihydrate, arginine hydrochloride, sodium citrate dihydrate, poloxamer 188
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

1 powder vial, 1 pre-filled syringe with 2.5 mL water for injections, 1 vial adapter, 1 butterfly needle, 2 alcohol swabs

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use after reconstitution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze. Store vial in the original package in order to protect from light.
Can be stored at room temperature (up to 25°C) for a single period of up to 1 month.

Taken out of refrigerator: _____

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Octapharma AB
Lars Forssells gata 23
112 75 Stockholm
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/936/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Nuwiq 250

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

POWDER VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Nuwiq 250 IU powder for solution for injection
simoctocog alfa (recombinant human coagulation factor VIII)
For intravenous use after reconstitution.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

Octapharma-Logo

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nuwiq 500 IU powder and solvent for solution for injection
simoctocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 Powder vial contains 500 IU simoctocog alfa (200 IU/mL after reconstitution).

3. LIST OF EXCIPIENTS

Excipients: Sucrose, sodium chloride, calcium chloride dihydrate, arginine hydrochloride, sodium citrate dihydrate, poloxamer 188
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

1 Powder vial, 1 pre-filled syringe with 2.5 mL water for injections, 1 vial adapter, 1 butterfly needle, 2 alcohol swabs

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use after reconstitution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze. Store vial in the original package in order to protect from light.
Can be stored at room temperature (up to 25°C) for a single period of up to 1 month.

Taken out of refrigerator: _____

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Octapharma AB
Lars Forssells gata 23
112 75 Stockholm
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/936/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Nuwiq 500

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

POWDER VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Nuwiq 500 IU powder for solution for injection
simoctocog alfa (recombinant human coagulation factor VIII)
For intravenous use after reconstitution.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

Octapharma-Logo

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nuwiq 1000 IU powder and solvent for solution for injection
simoctocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 Powder vial contains 1000 IU simoctocog alfa (400 IU/mL after reconstitution).

3. LIST OF EXCIPIENTS

Excipients: Sucrose, sodium chloride, calcium chloride dihydrate, arginine hydrochloride, sodium citrate dihydrate, poloxamer 188
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

1 Powder vial, 1 pre-filled syringe with 2.5 mL water for injections, 1 vial adapter, 1 butterfly needle, 2 alcohol swabs

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use after reconstitution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze. Store vial in the original package in order to protect from light.
Can be stored at room temperature (up to 25°C) for a single period of up to 1 month.

Taken out of refrigerator: _____

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Octapharma AB
Lars Forssells gata 23
112 75 Stockholm
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/936/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Nuwiq 1000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

POWDER VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Nuwiq 1000 IU powder for solution for injection
simoctocog alfa (recombinant human coagulation factor VIII)
For intravenous use after reconstitution.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

Octapharma-Logo

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nuwiq 1500 IU powder and solvent for solution for injection
simoctocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 Powder vial contains 1500 IU simoctocog alfa (600 IU/mL after reconstitution).

3. LIST OF EXCIPIENTS

Excipients: Sucrose, sodium chloride, calcium chloride dihydrate, arginine hydrochloride, sodium citrate dihydrate, poloxamer 188
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

1 Powder vial, 1 pre-filled syringe with 2.5 mL water for injections, 1 vial adapter, 1 butterfly needle, 2 alcohol swabs

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use after reconstitution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze. Store vial in the original package in order to protect from light.
Can be stored at room temperature (up to 25°C) for a single period of up to 1 month.
Taken out of refrigerator: _____

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Octapharma AB
Lars Forssells gata 23
112 75 Stockholm
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/936/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Nuwiq 1500

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

POWDER VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Nuwiq 1500 IU powder for solution for injection
simoctocog alfa (recombinant human coagulation factor VIII)
For intravenous use after reconstitution.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

Octapharma-Logo

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nuwiq 2000 IU powder and solvent for solution for injection
simoctocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 Powder vial contains 2000 IU simoctocog alfa (800 IU/mL after reconstitution).

3. LIST OF EXCIPIENTS

Excipients: Sucrose, sodium chloride, calcium chloride dihydrate, arginine hydrochloride, sodium citrate dihydrate, poloxamer 188
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

1 Powder vial, 1 pre-filled syringe with 2.5 mL water for injections, 1 vial adapter, 1 butterfly needle, 2 alcohol swabs

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use after reconstitution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze. Store vial in the original package in order to protect from light.

Can be stored at room temperature (up to 25°C) for a single period of up to 1 month.
Taken out of refrigerator: _____

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Octapharma AB
Lars Forssells gata 23
112 75 Stockholm
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/936/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Nuwiq 2000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

POWDER VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Nuwiq 2000 IU powder for solution for injection
simoctocog alfa (recombinant human coagulation factor VIII)
For intravenous use after reconstitution.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

Octapharma-Logo

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nuwiq 2500 IU powder and solvent for solution for injection
simoctocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 Powder vial contains 2500 IU simoctocog alfa (1000 IU/mL after reconstitution).

3. LIST OF EXCIPIENTS

Excipients: Sucrose, sodium chloride, calcium chloride dihydrate, arginine hydrochloride, sodium citrate dihydrate, poloxamer 188
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

1 Powder vial, 1 pre-filled syringe with 2.5 mL water for injections, 1 vial adapter, 1 butterfly needle, 2 alcohol swabs

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use after reconstitution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze. Store vial in the original package in order to protect from light.
Can be stored at room temperature (up to 25°C) for a single period of up to 1 month.

Taken out of refrigerator: _____

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Octapharma AB
Lars Forssells gata 23
112 75 Stockholm
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/936/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Nuwiq 2500

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

POWDER VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Nuwiq 2500 IU powder for solution for injection
simoctocog alfa (recombinant human coagulation factor VIII)
For intravenous use after reconstitution.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

Octapharma-Logo

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nuwiq 3000 IU powder and solvent for solution for injection
simoctocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 Powder vial contains 3000 IU simoctocog alfa (1200 IU/mL after reconstitution).

3. LIST OF EXCIPIENTS

Excipients: Sucrose, sodium chloride, calcium chloride dihydrate, arginine hydrochloride, sodium citrate dihydrate, poloxamer 188
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

1 Powder vial, 1 pre-filled syringe with 2.5 mL water for injections, 1 vial adapter, 1 butterfly needle, 2 alcohol swabs

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use after reconstitution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze. Store vial in the original package in order to protect from light.
Can be stored at room temperature (up to 25°C) for a single period of up to 1 month.

Taken out of refrigerator: _____

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Octapharma AB
Lars Forssells gata 23
112 75 Stockholm
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/936/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Nuwiq 3000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

POWDER VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Nuwiq 3000 IU powder for solution for injection
simoctocog alfa (recombinant human coagulation factor VIII)
For intravenous use after reconstitution.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

Octapharma-Logo

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nuwiq 4000 IU powder and solvent for solution for injection
simoctocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 Powder vial contains 4000 IU simoctocog alfa (1600 IU/mL after reconstitution).

3. LIST OF EXCIPIENTS

Excipients: Sucrose, sodium chloride, calcium chloride dihydrate, arginine hydrochloride, sodium citrate dihydrate, poloxamer 188
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

1 Powder vial, 1 pre-filled syringe with 2.5 mL water for injections, 1 vial adapter, 1 butterfly needle, 2 alcohol swabs

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use after reconstitution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze. Store vial in the original package in order to protect from light.
Can be stored at room temperature (up to 25°C) for a single period of up to 1 month.

Taken out of refrigerator: _____

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Octapharma AB
Lars Forssells gata 23
112 75 Stockholm
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/936/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Nuwiq 4000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

POWDER VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Nuwiq 4000 IU powder for solution for injection
simoctocog alfa (recombinant human coagulation factor VIII)
For intravenous use after reconstitution.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

Octapharma-Logo

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE WITH 2.5 ML WATER FOR INJECTIONS

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for Nuwiq
Water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.5 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Nuwiq 250 IU powder and solvent for solution for injection
Nuwiq 500 IU powder and solvent for solution for injection
Nuwiq 1000 IU powder and solvent for solution for injection
Nuwiq 1500 IU powder and solvent for solution for injection
Nuwiq 2000 IU powder and solvent for solution for injection
Nuwiq 2500 IU powder and solvent for solution for injection
Nuwiq 3000 IU powder and solvent for solution for injection
Nuwiq 4000 IU powder and solvent for solution for injection
simoctocog alfa (recombinant human coagulation factor VIII)

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. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Nuwiq is and what it is used for

Nuwiq contains the active substance human recombinant coagulation factor VIII (simoctocog alfa). Factor VIII is necessary for the blood to form clots and stop bleeding. In patients with haemophilia A (inborn factor VIII deficiency), factor VIII is missing or not working properly.
Nuwiq replaces the missing factor VIII and is used for treatment and prevention of bleeding in patients with haemophilia A and can be used for all age groups.

2. What you need to know before you use Nuwiq

Do not use Nuwiq
- if you are allergic to the active substance simoctocog alfa or any of the other ingredients of this medicine (listed in section 6).

If you are unsure about this, ask your doctor.

Warnings and precautions
Talk to your doctor before using Nuwiq.

There is a rare chance that you may experience an anaphylactic reaction (a severe, sudden allergic reaction) to Nuwiq. You should be aware of the early signs of allergic reactions as they are listed in section 4 “Allergic reactions”.
If any of these symptoms occur, stop the injection immediately and contact your doctor.

The formation of inhibitors (antibodies) is a known complication that can occur during treatment with all factor VIII medicines. These inhibitors, especially at high levels, stop the treatment working properly and you or your child will be monitored carefully for the development of these inhibitors. If you or your child´s bleeding is not being controlled with Nuwiq, tell your doctor immediately.

Cardiovascular events
In patients with existing cardiovascular risk factors, substitution therapy with FVIII may increase the cardiovascular risk.

Catheter-related complications
If you require a central venous access device (CVAD), risk of CVAD-related complications including local infections, presence of bacteria in the blood and catheter site thrombosis should be considered.

It is important to keep a record of the batch number of your Nuwiq.
So, every time you get a new package of Nuwiq, note down the date and the batch number (which is on the packaging after Lot) and keep this information in a safe place.

Other medicines and Nuwiq
Tell your doctor 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 for advice before using this medicine.

Driving and using machines
Nuwiq has no influence on your ability to drive and use machines.

Nuwiq contains sodium
This medicine contains 18.4 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 0.92 % of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use Nuwiq

Treatment with Nuwiq will be started by a doctor who is experienced in the care of patients with haemophilia A. Always use this medicine exactly as your doctor or nurse has told you. Check with your doctor or nurse if you are not sure.

Nuwiq is usually injected into a vein (intravenously) by your doctor or a nurse who are experienced in the care of patients with haemophilia A. You or someone else might also give your Nuwiq injection, but only after receiving adequate training.

Your doctor will calculate your dose of Nuwiq (in international units = IU) depending on your condition and body weight, and on whether it is used for prevention or treatment of bleeding. How often you need an injection will depend on how well Nuwiq is working for you. Usually, treatment for haemophilia A is a life-long treatment.

Prevention of bleeding
The usual dose of Nuwiq is 20 to 40 IU per kg body weight, given every 2 to 3 days. However, in some cases, especially in younger patients, more frequent injections or higher doses may be necessary.

Treatment of bleeding
The dose of Nuwiq is calculated depending on your body weight and the factor VIII levels to be achieved. The target factor VIII levels will depend on the severity and location of the bleeding.

If you have the impression that the effect of Nuwiq is insufficient, talk to your doctor. Your doctor will perform appropriate laboratory tests to make sure that you have adequate factor VIII levels. This is particularly important if you are having major surgery.

Patients developing factor VIII inhibitors
If your plasma factor VIII fails to reach expected levels with Nuwiq, or if bleeding is not adequately controlled, it could be due to the development of factor VIII inhibitors. This will be checked by your doctor. You might need a higher dose of Nuwiq or a different product to control bleedings. Do not increase the total dose of Nuwiq to control your bleeding without consulting your doctor.

Use in children and adolescents
The way Nuwiq is used in children and adolescents does not differ from the way it is used in adults. Because factor VIII products may have to be given more often in children and adolescents, a central venous access device (CVAD) may need to be fitted. A CVAD is an external connector that allows access to the bloodstream through a catheter without injection through the skin.

If you use more Nuwiq than you should
No symptoms of overdose have been reported. If you have injected more Nuwiq than you should, please inform your doctor.

If you forget to use Nuwiq
Do not take a double dose to make up for a forgotten dose. Proceed with the next dose immediately and continue as advised by your doctor.

If you stop using Nuwiq
Do not stop using Nuwiq without consulting your doctor.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

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

Please stop using this medicine immediately and seek urgent medical advice if:
- **you notice symptoms of allergic reactions**
  Allergic reactions may include rash, hives, urticaria (itchy rash), including generalized urticaria, swelling of lips and tongue, shortness of breath, wheezing, tightness of the chest, vomiting, restlessness, low blood pressure, and dizziness. These symptoms can be early symptoms of an anaphylactic shock. If severe, sudden allergic reactions (anaphylactic) occur (very rare: may affect up to 1 in 10,000 people), the injection must be stopped immediately, and you must contact your doctor right away. Severe symptoms require prompt emergency treatment.
- **you notice that the medicine stops working properly (bleeding is not stopped or becomes frequent)**
  For children and adolescents not previously treated with factor VIII medicines, inhibitor antibodies (see section 2) may form very commonly (more than 1 in 10 patients).
  However, for patients who have received previous treatment with factor VIII (more than 150 days of treatment) the risk is uncommon (less than 1 in 100 patients). If this happens, your or your child´s medicines may stop working properly and you or your child may experience persistent bleeding. If this happens, you should contact your doctor immediately.

Common side effects may affect up to 1 in 10 people
Hypersensitivity, fever.

Uncommon side effects may affect up to 1 in 100 people
Tingling or numbness (paraesthesia), headache, dizziness, vertigo, dyspnoea, dry mouth, back pain, injection site inflammation, injection site pain, a vague feeling of bodily discomfort (malaise), haemorrhagic anaemia, anaemia, chest pain, non-neutralising antibody positive (in previously treated patients).

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Nuwiq

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 vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C). Do not freeze. Store vial in the original package in order to protect from light.

Before the Nuwiq powder is reconstituted, it may be kept at room temperature (up to 25 °C) for a single period not exceeding 1 month. Record the date from when you start to store Nuwiq at room temperature on the product carton. Do not store Nuwiq in the refrigerator again after it has been stored at room temperature.
Use the reconstituted solution immediately after reconstitution.

Do not use the medicine in case you notice visible signs of deterioration of the tamper proof of packaging especially of the syringe and/or the vial.

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 Nuwiq contains
Powder:
- The active substance is recombinant human coagulation factor VIII (simoctocog alfa).
  Each powder vial contains 250, 500, 1000, 1500, 2000, 2500, 3000 or 4000 IU of simoctocog alfa.
  Each reconstituted solution contains approximately 100, 200, 400, 600, 800, 1000, 1200 or 1600 IU/mL of simoctocog alfa.
- The other ingredients are sucrose, sodium chloride, calcium chloride dihydrate, arginine hydrochloride, sodium citrate dihydrate and poloxamer 188. See section 2, “Nuwiq contains sodium”.

Solvent:
Water for injections

What Nuwiq looks like and contents of the pack
Nuwiq is provided as powder and solvent for solution for injection. The powder is a white to off-white powder in a glass vial. The solvent is water for injections in a glass pre-filled syringe.
After reconstitution, the solution is clear, colourless and free from foreign particles.

Each pack of Nuwiq contains:
- 1 powder vial with 250, 500, 1000, 1500, 2000, 2500, 3000 or 4000 IU simoctocog alfa
- 1 pre-filled syringe with 2.5 mL water for injections
- 1 vial adapter
- 1 butterfly needle
- 2 alcohol swabs

Marketing Authorisation Holder and Manufacturer
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Detailed information on this medicine is available on the web site of the European Medicines Agency: http://www.ema.europa.eu.

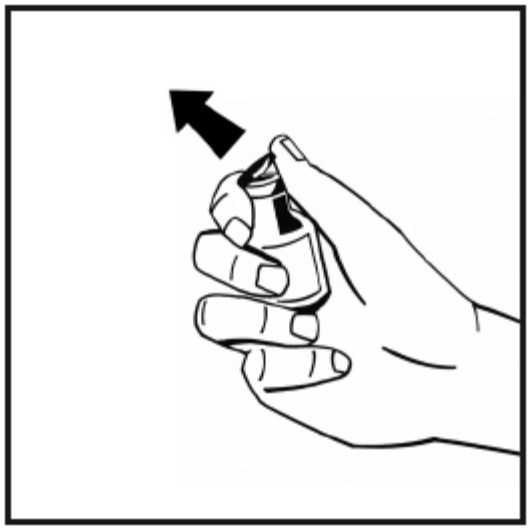
The following information is intended for healthcare professionals only:

On-demand treatment
The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case.
In the case of the following haemorrhagic events, 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.

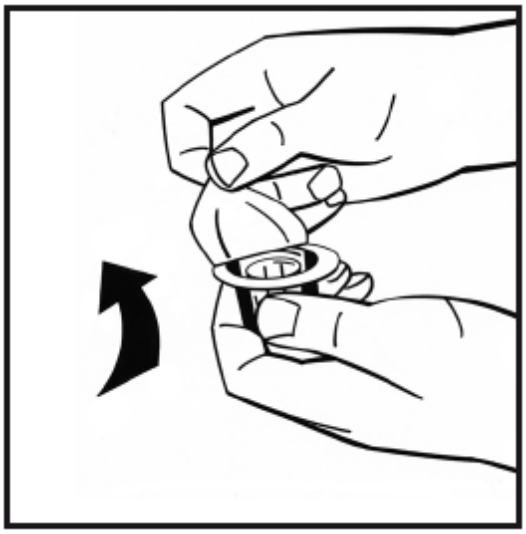
Degree of haemorrhage/ Type of surgical procedure	**Factor VIII level required (%) (IU/dL)**	**Frequency of doses (hours)/ Duration of therapy (days)**
Haemorrhage		
Early haemarthrosis, muscle bleeding or oral bleeding	20–40	Repeat every 12 to 24 hours. At least 1 day, until the bleeding episode as indicated by pain is resolved or healing is achieved.
More extensive haemarthrosis, muscle bleeding or haematoma	30–60	Repeat infusion every 12 to 24 hours for 3 to 4 days or more until pain and acute disability are resolved.
Life threatening haemorrhages	60–100	Repeat infusion every 8 to 24 hours until threat is resolved.
Surgery		
Minor surgery including tooth extraction	30–60	Every 24 hours, at least 1 day, until healing is achieved.
Major surgery	80–100 (pre- and postoperative)	Repeat infusion 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).

INSTRUCTIONS FOR PREPARATION AND ADMINISTRATION

1. Allow the solvent syringe (water for injections) and the powder in the closed vial to reach 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 pre-filled syringe. This temperature should be maintained during reconstitution.
2. Remove the plastic flip-off cap from the powder vial to expose the central portions of the rubber stopper. Do not remove the gray stopper or metal ring around the top of the vial.

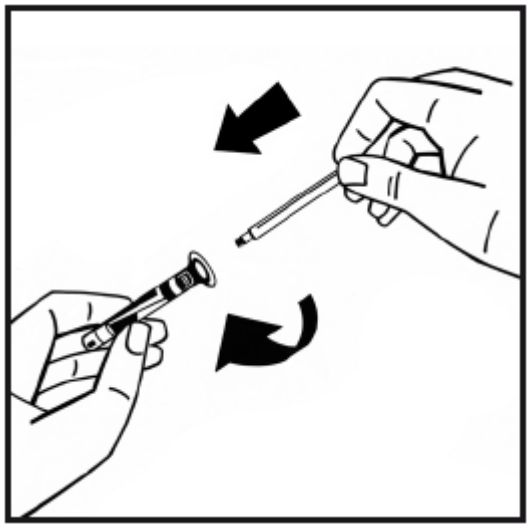


3. Wipe the top of the vial with an alcohol swab. Allow the alcohol to dry.
4. Peel back the paper cover from the vial adapter package. Do not remove the adapter from the package.

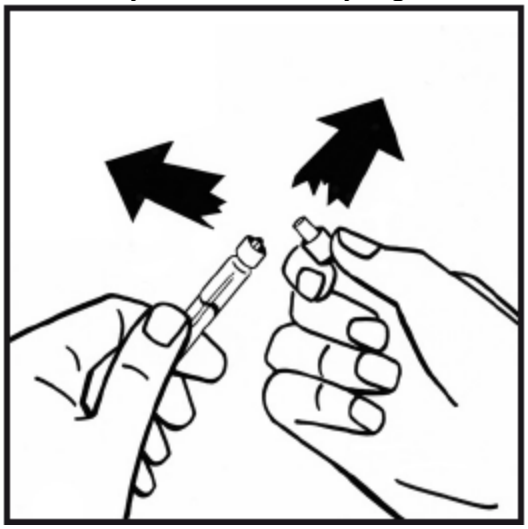


5. Place the powder vial on an even surface and hold it. Take the adapter package and place the vial adapter over the centre of the rubber stopper of the powder vial. Press down firmly the adapter package until the adapter spike penetrates the rubber stopper. The adapter snaps to the vial when done.

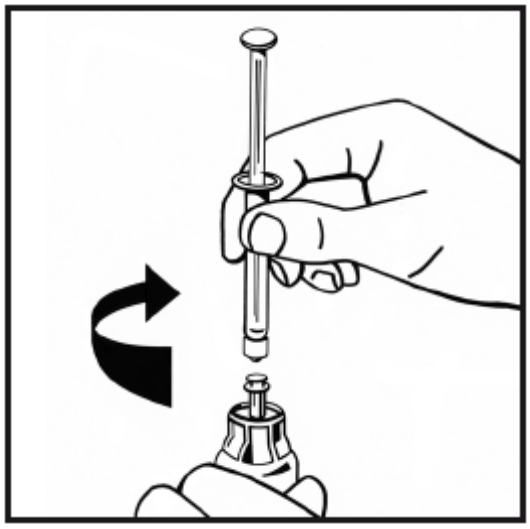
6. Peel back the paper cover from the pre-filled syringe package. Hold the plunger rod at the end and do not touch the shaft. Attach the threaded end of the plunger rod to the solvent syringe plunger. Turn the plunger rod clockwise until a slight resistance is felt.



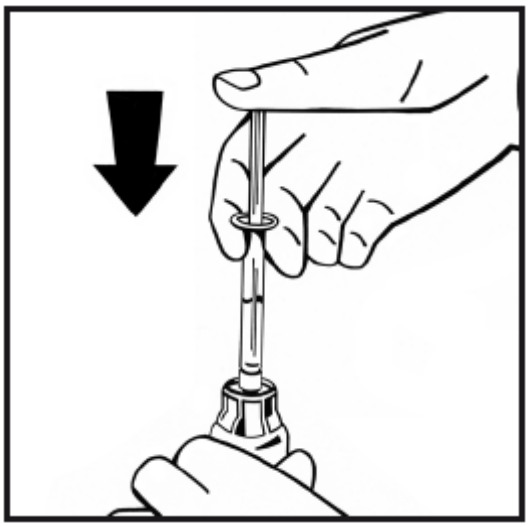
7. Break off the tamper-proof plastic tip from the solvent syringe by snapping the perforation of the cap. Do not touch the inside of the cap or the syringe tip. In case the solution is not used immediately close the filled syringe with the tamper-proof plastic tip for storage.



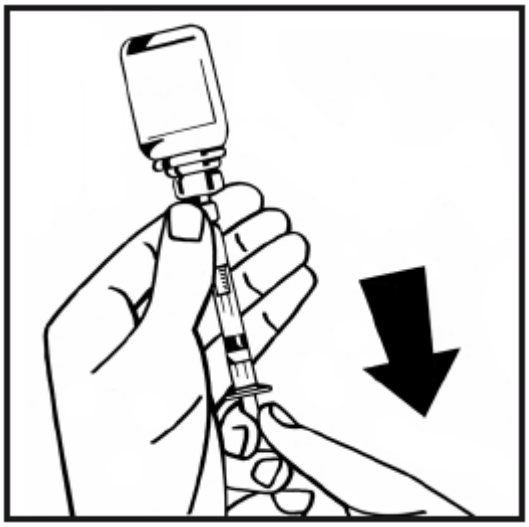
8. Remove the adapter packaging and discard.
9. Firmly connect the solvent syringe to the vial adapter by turning clockwise until resistance is felt.



10. Slowly inject all solvent into the powder vial by pressing down the plunger rod.



11. Without removing the syringe, gently move or swirl the vial in circles a few times to dissolve the powder. Do not shake. Wait until all the powder dissolves completely.
12. Visually inspect the final solution for particles before administration. The solution should be clear and colourless, practically free from visible particles. Do not use solutions that are cloudy or have deposits.
13. Turn the vial attached to the syringe upside down, and slowly draw the final solution into the syringe. Make sure that the entire content of the vial is transferred to the syringe.



14. Detach the filled syringe from the vial adapter by turning counter clockwise and discard the empty vial.

15. The solution is now prepared for immediate use. Do not refrigerate.
16. Clean the chosen injection site with one of the provided alcohol swabs.
17. Attach the provided infusion set to the syringe.
    Insert the needle of the infusion set into the chosen vein. If you have used a tourniquet to make the vein easier to see, this tourniquet should be released before you start injecting the solution. No blood must flow into the syringe due to the risk of formation of fibrin clots.
18. Inject the solution into the vein at a slow speed, not faster than 4 mL per minute.

If you use more than one vial of powder for one treatment, you may use the same injection needle again. The vial adapter and the syringe are for single use only.