

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Nuwiq 250 IU powder and solvent for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains nominally 250 IU human coagulation factor VIII (rDNA), simoctocog alfa.

Nuwiq contains approximately 100 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(s) with known effect:

7.35 mg sodium per ml reconstituted solution (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: water for injections, 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.

Previously untreated patients

The safety and efficacy of Nuwiq in previously untreated patients have not yet been established.

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 standard for factor VIII products. Factor VIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or 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:

- I. Required units = body weight (kg) x desired factor VIII rise (%) (IU/dl) x 0.5 (IU/kg per IU/dl)
- II. 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)
<u>Haemorrhage</u>		
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.
<u>Surgery</u>		
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. In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

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. 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, demonstrating different half-lives and recoveries.

Paediatric population

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

No data are available in children below the age of 2 years.

Method of administration

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

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 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, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days.

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 patients carefully for inhibitor occurrence following any product switch.

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, such as immune tolerance induction (ITI), should be considered. Management of such patients should be directed by physicians with experience in the care of haemophilia and factor VIII inhibitors.

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.

It is strongly recommended that every time that Nuwiq 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.

Paediatric population

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

Excipient related considerations (sodium content)

This medicinal product contains less than 1 mmol sodium (23 mg) per vial. However depending on the body weight and posology, the patient could receive more than one vial. This should be taken into consideration by patients on a controlled sodium diet.

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

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 be contacted.

Tabulated list of adverse reactions

During clinical studies with Nuwiq in previously treated paediatric (2 to 11 years, n = 58), adolescent (12 to 17 years, n = 3) and adult patients (n = 74) with severe haemophilia A, a total of 8 adverse drug reactions (ADRs) (6 in adults, 2 in children) were reported in 5 patients (3 adults, 2 children).

Table 1 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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 occurring per patient of adverse drug reactions (ADRs) in clinical trials in 135 previously treated patients with severe haemophilia A

MedDRA Standard System Organ Class	Adverse reactions	Frequency*
Nervous system disorders	Parasthesia Headache	Uncommon
Ear and labyrinth disorders	Vertigo	Uncommon
Gastrointestinal disorders	Dry mouth	Uncommon
Musculoskeletal and connective tissue disorders	Back pain	Uncommon
General disorders and administration site conditions	Injection site inflammation Injection site pain	Uncommon
Investigations	Non-neutralising anti factor VIII antibody positive	Uncommon

* All these ADRs occurred only once. As the total number of studied patients is 135, the frequency cannot be less than “uncommon” if an ADR occurs once.

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 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: Antihæmorrhagics: 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 hæmophilic 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.

The immunogenicity of Nuwiq was evaluated in clinical trials in 135 previously treated patients with severe hæmophilia A (74 adult and 61 paediatric patients). None of the patients developed inhibitors.

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

Paediatric population

Data have been 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).

The European Medicines Agency has deferred the obligation to submit the results of studies with Nuwiq in one or more subsets of the paediatric population in treatment of Haemophilia A (congenital Factor VIII deficiency) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Table 2. PK parameters for Nuwiq (Dose: 50 IU/kg) in adult previously treated patients (age 18-65 years) with severe hæmophilia 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)
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/m², Pre-adipose: BMI 25-30 kg/m², Adipose: BMI > 30 kg/m², SD = Standard deviation

5.3 Preclinical safety data

In preclinical 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

2 years

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.

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

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Each pack of Nuwiq 250 IU contains:

- Powder: 250 IU powder in 8 ml type 1 glass vial, closed with coated bromobutyl stopper and sealed with aluminium flip-off cap
- Solvent: 2.5 ml water for injections in a pre-filled borosilicate glass syringe

- 1 sterile vial adapter for reconstitution with 1 butterfly needle and 2 alcohol swabs

Pack size of 1.

Not all pack sizes may be marketed.

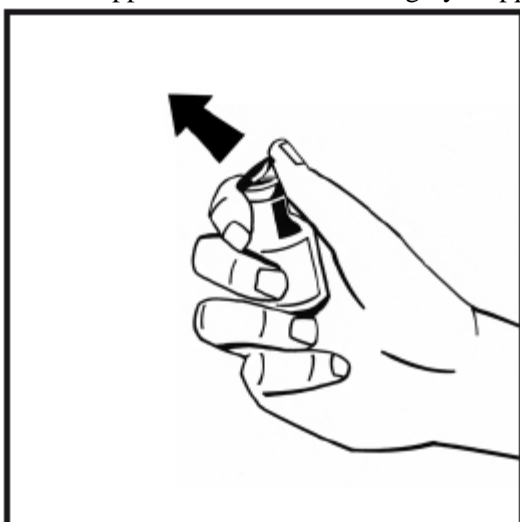
6.6 Special precautions for disposal and other handling

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.

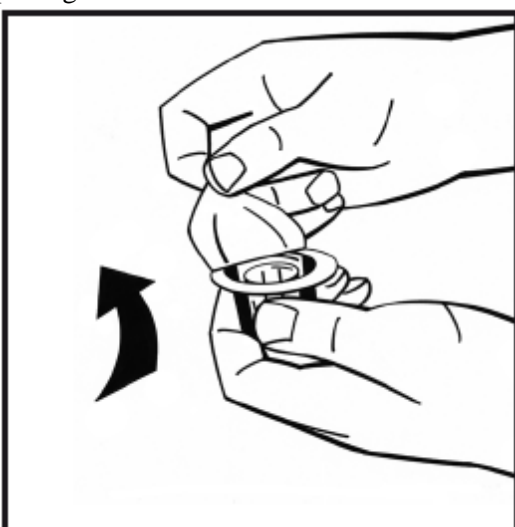
Reconstituted medicinal product should be inspected visually for particulate matter and discoloration prior to administration. The reconstituted medicinal product is a clear, colourless solution, free from foreign particles and has a pH of 6.5 to 7.5. Do not use solutions that are cloudy or have deposits.

Instructions for preparation and administration

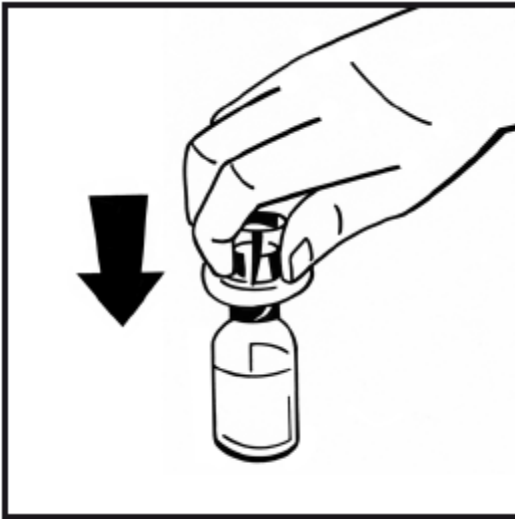
1. Allow the solvent syringe (water for injections) and the powder in the closed vial to reach room temperature. You can do this by holding them in your hands until they feel as warm as your hands. Do not use any other way to heat the vial and pre-filled syringe. This temperature should be maintained during reconstitution.
2. Remove the plastic flip-top cap from the powder vial to expose the central portions of the rubber stopper. Do not remove the grey stopper or metal ring around the top of the vial.



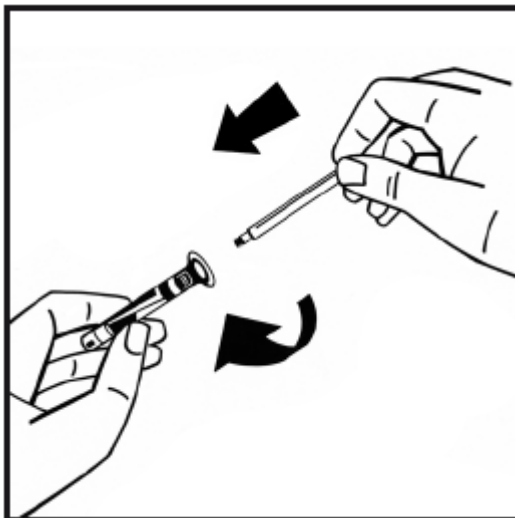
3. Wipe the top of the vial with an alcohol swab. Allow the alcohol to dry.
4. Peel back the paper cover from the vial adapter package. Do not remove the adapter from the package.



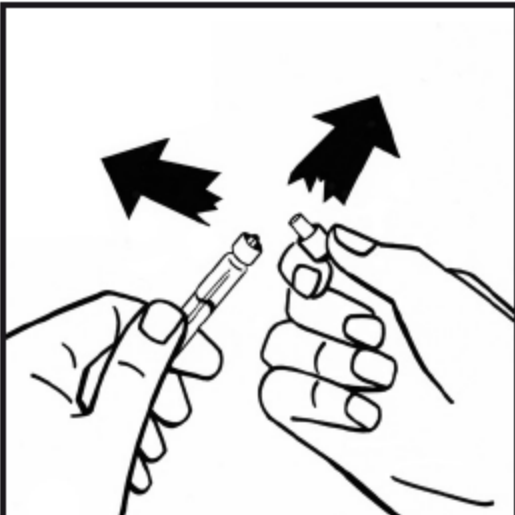
5. Place the powder vial on an even surface and hold it. Take the adapter package and place the vial adapter over the centre of the rubber stopper of the powder vial. Press down firmly the adapter package until the adapter spike penetrates the rubber stopper. The adapter snaps to the vial when done.



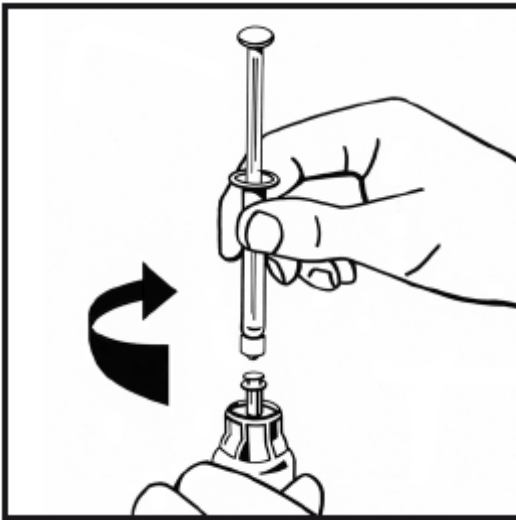
6. Peel back the paper cover from the pre-filled syringe package. Hold the plunger rod at the end and do not touch the shaft. Attach the threaded end of the plunger rod to the solvent syringe plunger. Turn the plunger rod clockwise until a slight resistance is felt.



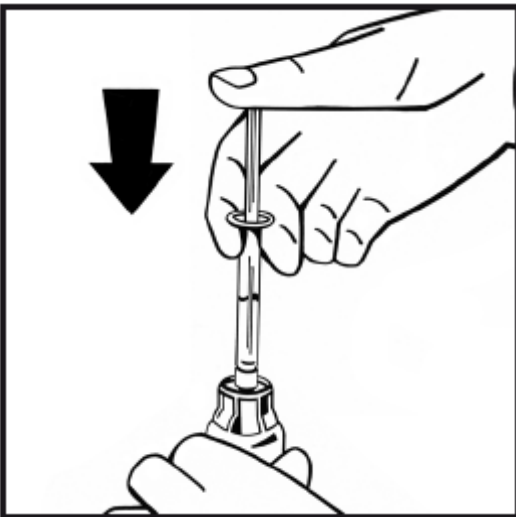
7. Break off the tamper-proof plastic tip from the solvent syringe by snapping the perforation of the cap. Do not touch the inside of the cap or the syringe tip. In case the solution is not used immediately close the filled syringe with the tamper-proof plastic tip for storage.



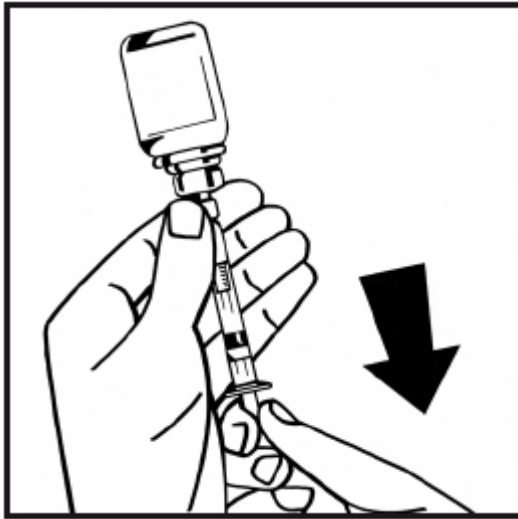
8. Remove the adapter packaging and discard.
9. Firmly connect the solvent syringe to the vial adapter by turning clockwise until resistance is felt.



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
Elersvägen 40
112 75 Stockholm
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/A/14/936/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

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>.

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For the full list of excipients, see section 6.1.

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

Nuwiq can be used for all age groups.

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

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The safety and efficacy of Nuwiq in previously untreated patients have not yet been established.

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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.

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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:

$$\text{III. Required units} = \text{body weight (kg)} \times \text{desired factor VIII rise (\%)} \text{ (IU/dl)} \times 0.5 \text{ (IU/kg per IU/dl)}$$

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

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)
<u>Haemorrhage</u>		
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.
<u>Surgery</u>		
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. In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

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. 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, demonstrating different half-lives and recoveries.

Paediatric population

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

No data are available in children below the age of 2 years.

Method of administration

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

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 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, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days.

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 patients carefully for inhibitor occurrence following any product switch.

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, such as immune tolerance induction (ITI), should be considered. Management of such patients should be directed by physicians with experience in the care of haemophilia and factor VIII inhibitors.

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.

It is strongly recommended that every time that Nuwiq 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.

Paediatric population

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

Excipient related considerations (sodium content)

This medicinal product contains less than 1 mmol sodium (23 mg) per vial. However depending on the body weight and posology, the patient could receive more than one vial. This should be taken into consideration by patients on a controlled sodium diet.

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

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 be contacted.

Tabulated list of adverse reactions

During clinical studies with Nuwiq in previously treated paediatric (2 to 11 years, n = 58), adolescent (12 to 17 years, n = 3) and adult patients (n = 74) with severe haemophilia A, a total of 8 adverse drug reactions (ADRs) (6 in adults, 2 in children) were reported in 5 patients (3 adults, 2 children).

Table 1 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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 6. Frequency of occurring per patient of adverse drug reactions (ADRs) in clinical trials in 135 previously treated patients with severe haemophilia A

MedDRA Standard System Organ Class	Adverse reactions	Frequency*
Nervous system disorders	Parasthesia Headache	Uncommon
Ear and labyrinth disorders	Vertigo	Uncommon
Gastrointestinal disorders	Dry mouth	Uncommon
Musculoskeletal and connective tissue disorders	Back pain	Uncommon
General disorders and administration site conditions	Injection site inflammation Injection site pain	Uncommon
Investigations	Non-neutralising anti factor VIII antibody positive	Uncommon

* All these ADRs occurred only once. As the total number of studied patients is 135, the frequency cannot be less than “uncommon” if an ADR occurs once.

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 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: Antihæmorrhagics: 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 hæmophilic 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.

The immunogenicity of Nuwiq was evaluated in clinical trials in 135 previously treated patients with severe hæmophilia A (74 adult and 61 paediatric patients). None of the patients developed inhibitors.

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

Paediatric population

Data have been 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).

The European Medicines Agency has deferred the obligation to submit the results of studies with Nuwiq in one or more subsets of the paediatric population in treatment of Haemophilia A (congenital Factor VIII deficiency) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Table 7. PK parameters for Nuwiq (Dose: 50 IU/kg) in adult previously treated patients (age 18-65 years) with severe hæmophilia 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 8. 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 9. 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)
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 10. 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/m², Pre-adipose: BMI 25-30 kg/m², Adipose: BMI > 30 kg/m², SD = Standard deviation

5.3 Preclinical safety data

In preclinical 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

2 years

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.

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

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Each pack of Nuwiq 500 IU contains:

- Powder: 500 IU powder in 8 ml type 1 glass vial, closed with coated bromobutyl stopper and sealed with aluminium flip-off cap
- Solvent: 2.5 ml water for injections in a pre-filled borosilicate glass syringe

- 1 sterile vial adapter for reconstitution with 1 butterfly needle and 2 alcohol swabs

Pack size of 1.

Not all pack sizes may be marketed.

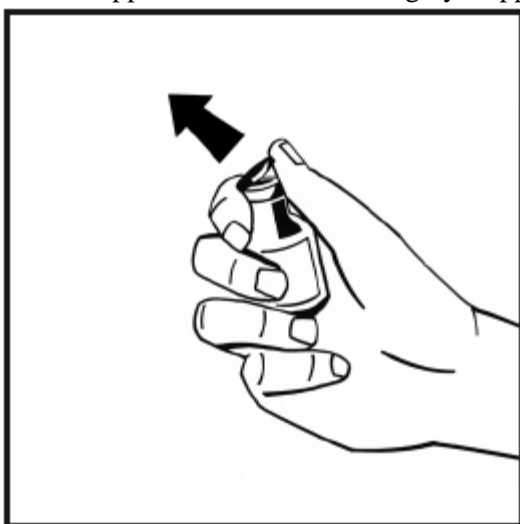
6.6 Special precautions for disposal and other handling

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.

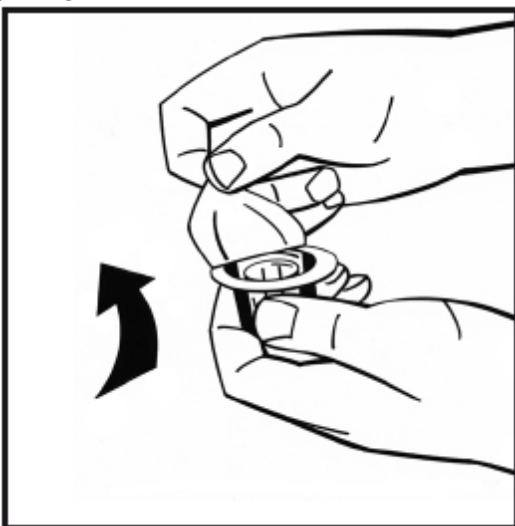
Reconstituted medicinal product should be inspected visually for particulate matter and discoloration prior to administration. The reconstituted medicinal product is a clear, colourless solution, free from foreign particles and has a pH of 6.5 to 7.5. Do not use solutions that are cloudy or have deposits.

Instructions for preparation and administration

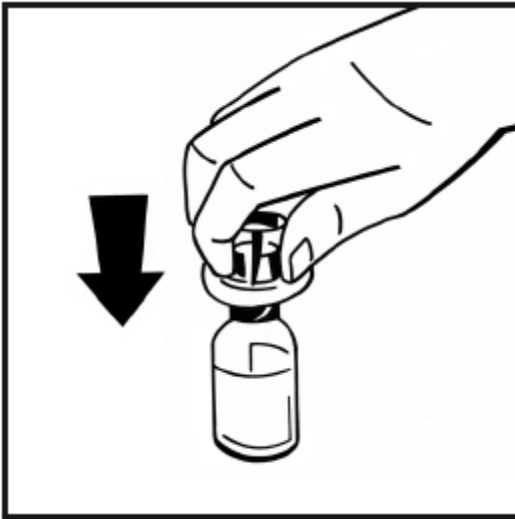
1. Allow the solvent syringe (water for injections) and the powder in the closed vial to reach room temperature. You can do this by holding them in your hands until they feel as warm as your hands. Do not use any other way to heat the vial and pre-filled syringe. This temperature should be maintained during reconstitution.
2. Remove the plastic flip-top cap from the powder vial to expose the central portions of the rubber stopper. Do not remove the grey stopper or metal ring around the top of the vial.



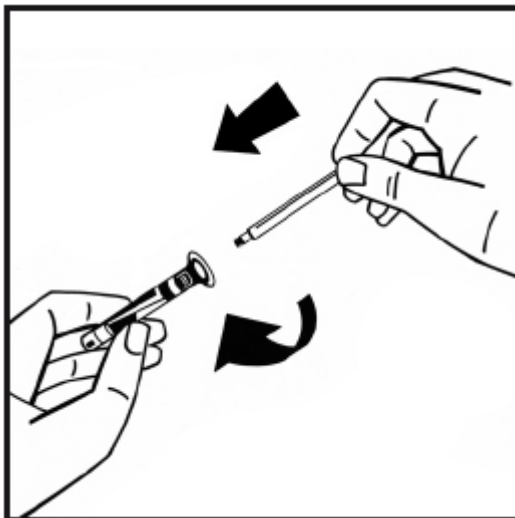
3. Wipe the top of the vial with an alcohol swab. Allow the alcohol to dry.
4. Peel back the paper cover from the vial adapter package. Do not remove the adapter from the package.



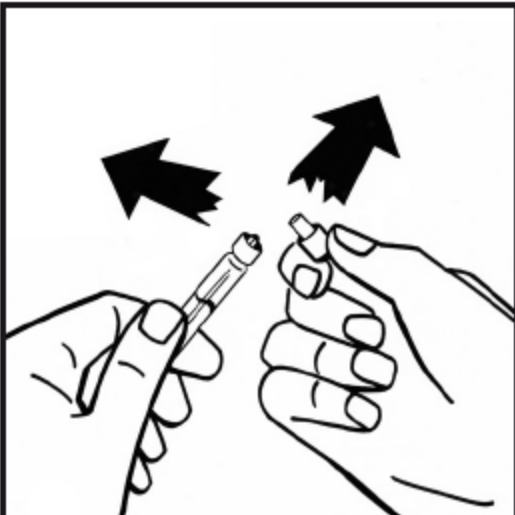
5. Place the powder vial on an even surface and hold it. Take the adapter package and place the vial adapter over the centre of the rubber stopper of the powder vial. Press down firmly the adapter package until the adapter spike penetrates the rubber stopper. The adapter snaps to the vial when done.



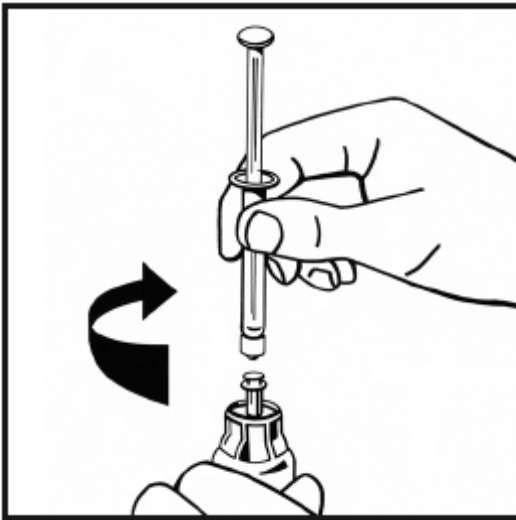
6. Peel back the paper cover from the pre-filled syringe package. Hold the plunger rod at the end and do not touch the shaft. Attach the threaded end of the plunger rod to the solvent syringe plunger. Turn the plunger rod clockwise until a slight resistance is felt.



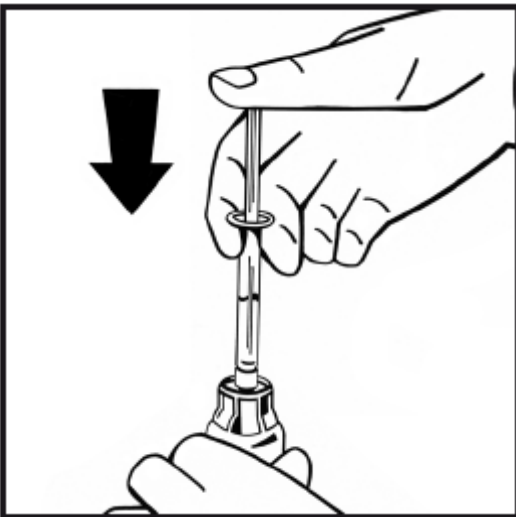
7. Break off the tamper-proof plastic tip from the solvent syringe by snapping the perforation of the cap. Do not touch the inside of the cap or the syringe tip. In case the solution is not used immediately close the filled syringe with the tamper-proof plastic tip for storage.



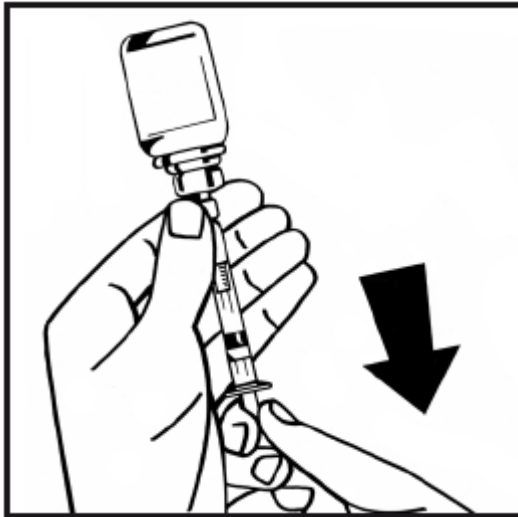
8. Remove the adapter packaging and discard.
9. Firmly connect the solvent syringe to the vial adapter by turning clockwise until resistance is felt.



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
Elersvägen 40
112 75 Stockholm
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/A/14/936/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

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>.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Nuwiq 1000 IU powder and solvent for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains nominally 1000 IU human coagulation factor VIII (rDNA), simoctocog alfa.

Nuwiq contains approximately 400 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(s) with known effect:

7.35 mg sodium per ml reconstituted solution (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: water for injections, 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.

Previously untreated patients

The safety and efficacy of Nuwiq in previously untreated patients have not yet been established.

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 standard for factor VIII products. Factor VIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or 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:

$$\text{V. Required units} = \text{body weight (kg)} \times \text{desired factor VIII rise (\%)} \text{ (IU/dl)} \times 0.5 \text{ (IU/kg per IU/dl)}$$

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

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)
<u>Haemorrhage</u>		
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.
<u>Surgery</u>		
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. In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

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. 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, demonstrating different half-lives and recoveries.

Paediatric population

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

No data are available in children below the age of 2 years.

Method of administration

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

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 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, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days.

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 patients carefully for inhibitor occurrence following any product switch.

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, such as immune tolerance induction (ITI), should be considered. Management of such patients should be directed by physicians with experience in the care of haemophilia and factor VIII inhibitors.

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.

It is strongly recommended that every time that Nuwiq 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.

Paediatric population

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

Excipient related considerations (sodium content)

This medicinal product contains less than 1 mmol sodium (23 mg) per vial. However depending on the body weight and posology, the patient could receive more than one vial. This should be taken into consideration by patients on a controlled sodium diet.

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

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 be contacted.

Tabulated list of adverse reactions

During clinical studies with Nuwiq in previously treated paediatric (2 to 11 years, n = 58), adolescent (12 to 17 years, n = 3) and adult patients (n = 74) with severe haemophilia A, a total of 8 adverse drug reactions (ADRs) (6 in adults, 2 in children) were reported in 5 patients (3 adults, 2 children).

Table 1 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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 11. Frequency of occurring per patient of adverse drug reactions (ADRs) in clinical trials in 135 previously treated patients with severe haemophilia A

MedDRA Standard System Organ Class	Adverse reactions	Frequency*
Nervous system disorders	Parasthesia Headache	Uncommon
Ear and labyrinth disorders	Vertigo	Uncommon
Gastrointestinal disorders	Dry mouth	Uncommon
Musculoskeletal and connective tissue disorders	Back pain	Uncommon
General disorders and administration site conditions	Injection site inflammation Injection site pain	Uncommon
Investigations	Non-neutralising anti factor VIII antibody positive	Uncommon

* All these ADRs occurred only once. As the total number of studied patients is 135, the frequency cannot be less than “uncommon” if an ADR occurs once.

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 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: Antihæmorrhagics: 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 hæmophilic 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.

The immunogenicity of Nuwiq was evaluated in clinical trials in 135 previously treated patients with severe hæmophilia A (74 adult and 61 paediatric patients). None of the patients developed inhibitors.

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

Paediatric population

Data have been 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).

The European Medicines Agency has deferred the obligation to submit the results of studies with Nuwiq in one or more subsets of the paediatric population in treatment of Haemophilia A (congenital Factor VIII deficiency) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Table 12. PK parameters for Nuwiq (Dose: 50 IU/kg) in adult previously treated patients (age 18-65 years) with severe hæmophilia 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 13. 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 14. 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)
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 15. 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/m², Pre-adipose: BMI 25-30 kg/m², Adipose: BMI > 30 kg/m², SD = Standard deviation

5.3 Preclinical safety data

In preclinical 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

2 years

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.

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

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Each pack of Nuwiq 1000 IU contains:

- Powder: 1000 IU powder in 8 ml type 1 glass vial, closed with coated bromobutyl stopper and sealed with aluminium flip-off cap
- Solvent: 2.5 ml water for injections in a pre-filled borosilicate glass syringe

- 1 sterile vial adapter for reconstitution with 1 butterfly needle and 2 alcohol swabs

Pack size of 1.

Not all pack sizes may be marketed.

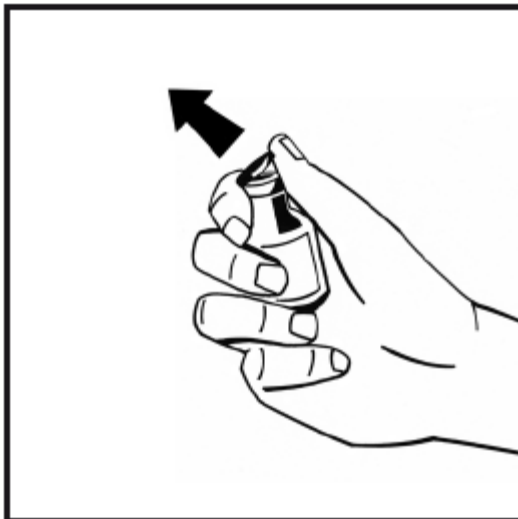
6.6 Special precautions for disposal and other handling

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.

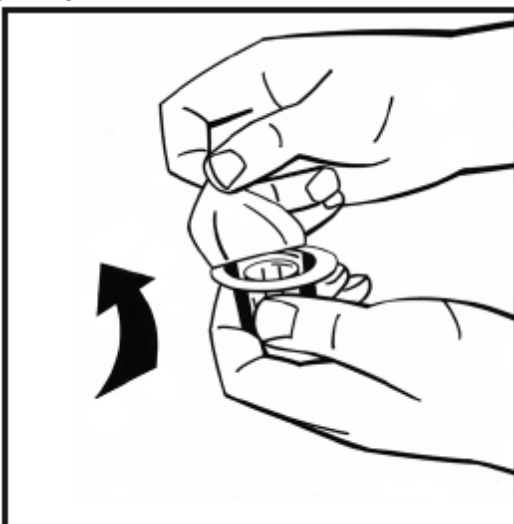
Reconstituted medicinal product should be inspected visually for particulate matter and discoloration prior to administration. The reconstituted medicinal product is a clear, colourless solution, free from foreign particles and has a pH of 6.5 to 7.5. Do not use solutions that are cloudy or have deposits.

Instructions for preparation and administration

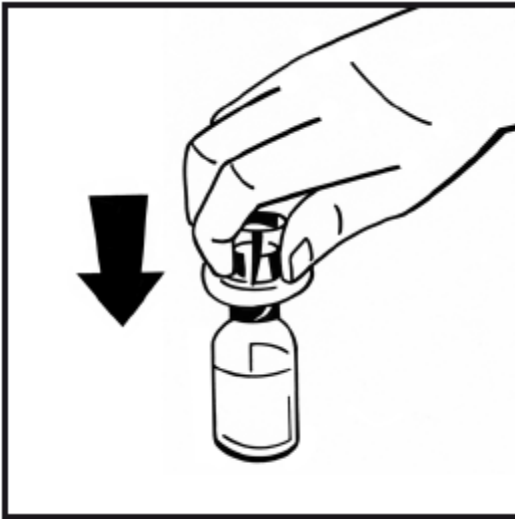
1. Allow the solvent syringe (water for injections) and the powder in the closed vial to reach room temperature. You can do this by holding them in your hands until they feel as warm as your hands. Do not use any other way to heat the vial and pre-filled syringe. This temperature should be maintained during reconstitution.
2. Remove the plastic flip-top cap from the powder vial to expose the central portions of the rubber stopper. Do not remove the grey stopper or metal ring around the top of the vial.



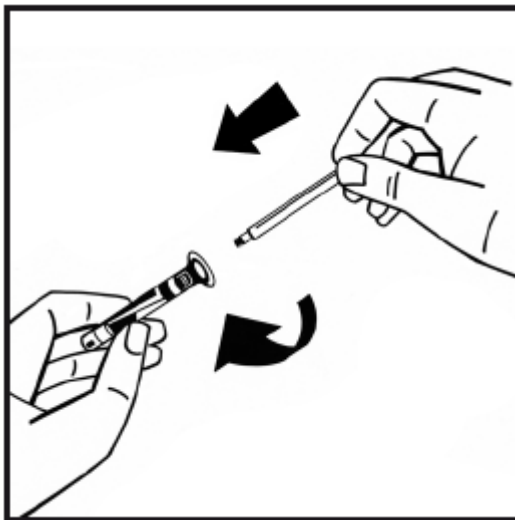
3. Wipe the top of the vial with an alcohol swab. Allow the alcohol to dry.
4. Peel back the paper cover from the vial adapter package. Do not remove the adapter from the package.



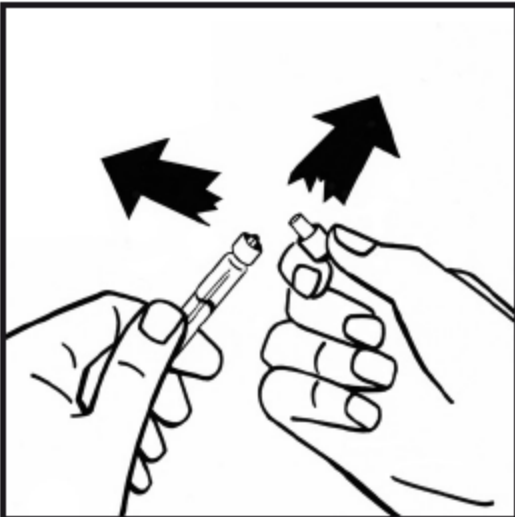
5. Place the powder vial on an even surface and hold it. Take the adapter package and place the vial adapter over the centre of the rubber stopper of the powder vial. Press down firmly the adapter package until the adapter spike penetrates the rubber stopper. The adapter snaps to the vial when done.



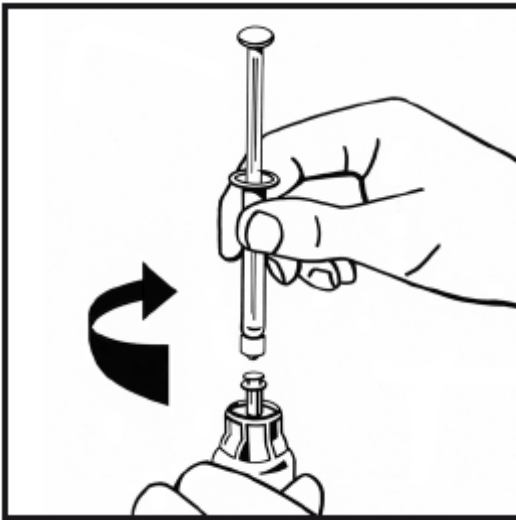
6. Peel back the paper cover from the pre-filled syringe package. Hold the plunger rod at the end and do not touch the shaft. Attach the threaded end of the plunger rod to the solvent syringe plunger. Turn the plunger rod clockwise until a slight resistance is felt.



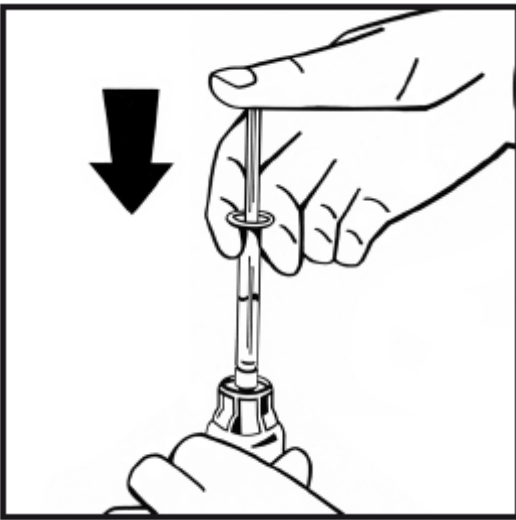
7. Break off the tamper-proof plastic tip from the solvent syringe by snapping the perforation of the cap. Do not touch the inside of the cap or the syringe tip. In case the solution is not used immediately close the filled syringe with the tamper-proof plastic tip for storage.



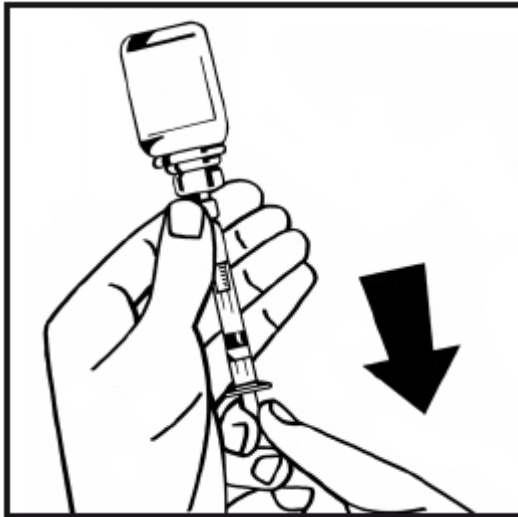
8. Remove the adapter packaging and discard.
9. Firmly connect the solvent syringe to the vial adapter by turning clockwise until resistance is felt.



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
Elersvägen 40
112 75 Stockholm
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/A/14/936/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

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>.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Nuwiq 2000 IU powder and solvent for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains nominally 2000 IU human coagulation factor VIII (rDNA), simoctocog alfa.

Nuwiq contains approximately 800 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(s) with known effect:

7.35 mg sodium per ml reconstituted solution (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: water for injections, 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.

Previously untreated patients

The safety and efficacy of Nuwiq in previously untreated patients have not yet been established.

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 standard for factor VIII products. Factor VIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or 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:

$$\text{VII. Required units} = \text{body weight (kg)} \times \text{desired factor VIII rise (\%)} \text{ (IU/dl)} \times 0.5 \text{ (IU/kg per IU/dl)}$$

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

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)
<u>Haemorrhage</u>		
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.
<u>Surgery</u>		
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. In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

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. 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, demonstrating different half-lives and recoveries.

Paediatric population

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

No data are available in children below the age of 2 years.

Method of administration

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

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 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, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days.

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 patients carefully for inhibitor occurrence following any product switch.

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, such as immune tolerance induction (ITI), should be considered. Management of such patients should be directed by physicians with experience in the care of haemophilia and factor VIII inhibitors.

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.

It is strongly recommended that every time that Nuwiq 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.

Paediatric population

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

Excipient related considerations (sodium content)

This medicinal product contains less than 1 mmol sodium (23 mg) per vial. However depending on the body weight and posology, the patient could receive more than one vial. This should be taken into consideration by patients on a controlled sodium diet.

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

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 be contacted.

Tabulated list of adverse reactions

During clinical studies with Nuwiq in previously treated paediatric (2 to 11 years, n = 58), adolescent (12 to 17 years, n = 3) and adult patients (n = 74) with severe haemophilia A, a total of 8 adverse drug reactions (ADRs) (6 in adults, 2 in children) were reported in 5 patients (3 adults, 2 children).

Table 1 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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 16. Frequency of occurring per patient of adverse drug reactions (ADRs) in clinical trials in 135 previously treated patients with severe haemophilia A

MedDRA Standard System Organ Class	Adverse reactions	Frequency*
Nervous system disorders	Parasthesia Headache	Uncommon
Ear and labyrinth disorders	Vertigo	Uncommon
Gastrointestinal disorders	Dry mouth	Uncommon
Musculoskeletal and connective tissue disorders	Back pain	Uncommon
General disorders and administration site conditions	Injection site inflammation Injection site pain	Uncommon
Investigations	Non-neutralising anti factor VIII antibody positive	Uncommon

* All these ADRs occurred only once. As the total number of studied patients is 135, the frequency cannot be less than “uncommon” if an ADR occurs once.

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 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: Antihæmorrhagics: 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 hæmophilic 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.

The immunogenicity of Nuwiq was evaluated in clinical trials in 135 previously treated patients with severe hæmophilia A (74 adult and 61 paediatric patients). None of the patients developed inhibitors.

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

Paediatric population

Data have been 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).

The European Medicines Agency has deferred the obligation to submit the results of studies with Nuwiq in one or more subsets of the paediatric population in treatment of Haemophilia A (congenital Factor VIII deficiency) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Table 17. PK parameters for Nuwiq (Dose: 50 IU/kg) in adult previously treated patients (age 18-65 years) with severe hæmophilia 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 18. 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 19. 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)
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 20. 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/m², Pre-adipose: BMI 25-30 kg/m², Adipose: BMI > 30 kg/m², SD = Standard deviation

5.3 Preclinical safety data

In preclinical 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

2 years

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.

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

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Each pack of Nuwiq 2000 IU contains:

- Powder: 2000 IU powder in 8 ml type 1 glass vial, closed with coated bromobutyl stopper and sealed with aluminium flip-off cap
- Solvent: 2.5 ml water for injections in a pre-filled borosilicate glass syringe

- 1 sterile vial adapter for reconstitution with 1 butterfly needle and 2 alcohol swabs

Pack size of 1.

Not all pack sizes may be marketed.

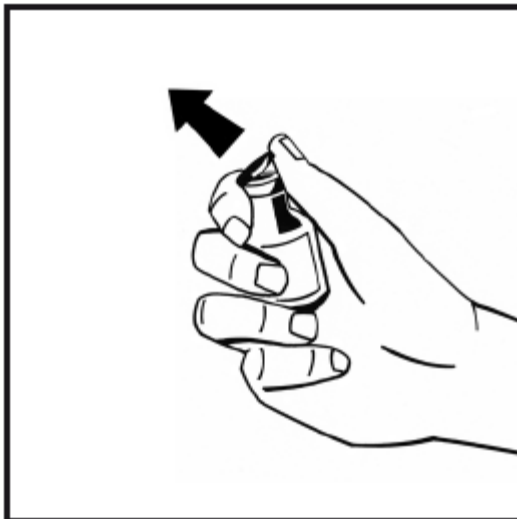
6.6 Special precautions for disposal and other handling

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.

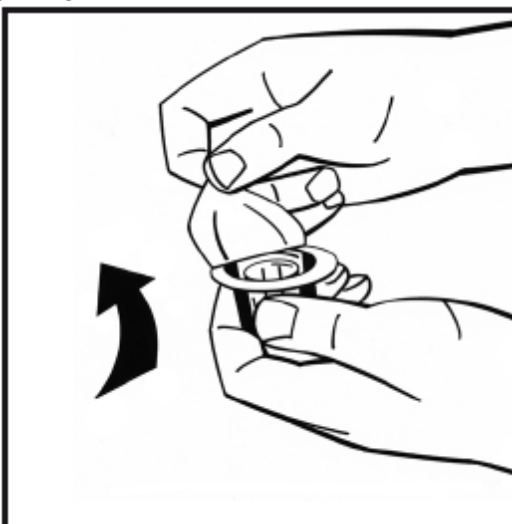
Reconstituted medicinal product should be inspected visually for particulate matter and discoloration prior to administration. The reconstituted medicinal product is a clear, colourless solution, free from foreign particles and has a pH of 6.5 to 7.5. Do not use solutions that are cloudy or have deposits.

Instructions for preparation and administration

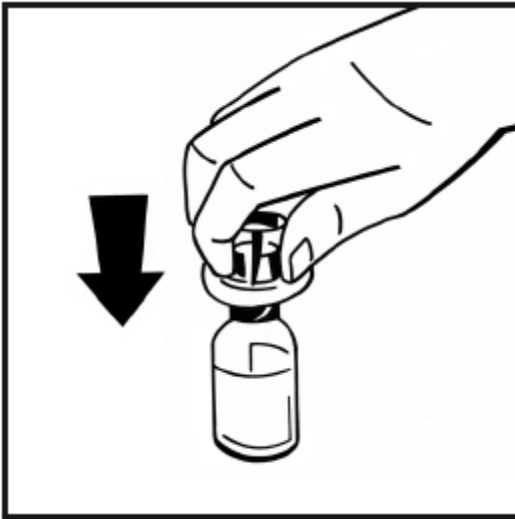
1. Allow the solvent syringe (water for injections) and the powder in the closed vial to reach room temperature. You can do this by holding them in your hands until they feel as warm as your hands. Do not use any other way to heat the vial and pre-filled syringe. This temperature should be maintained during reconstitution.
2. Remove the plastic flip-top cap from the powder vial to expose the central portions of the rubber stopper. Do not remove the grey stopper or metal ring around the top of the vial.



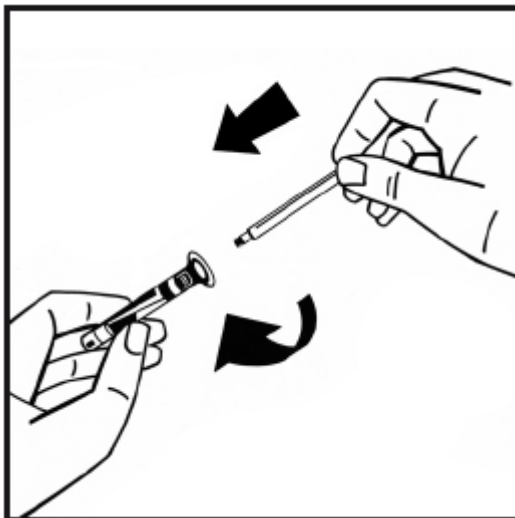
3. Wipe the top of the vial with an alcohol swab. Allow the alcohol to dry.
4. Peel back the paper cover from the vial adapter package. Do not remove the adapter from the package.



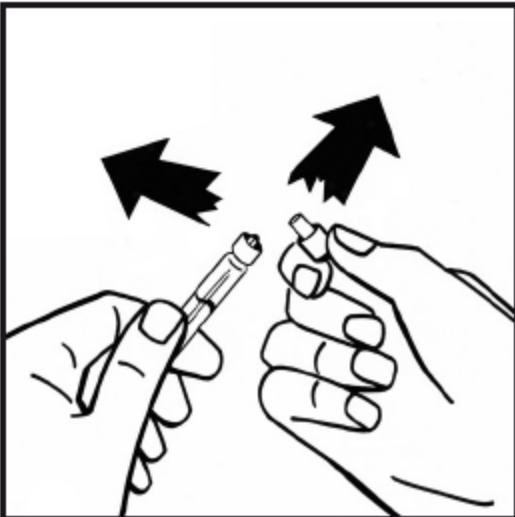
5. Place the powder vial on an even surface and hold it. Take the adapter package and place the vial adapter over the centre of the rubber stopper of the powder vial. Press down firmly the adapter package until the adapter spike penetrates the rubber stopper. The adapter snaps to the vial when done.



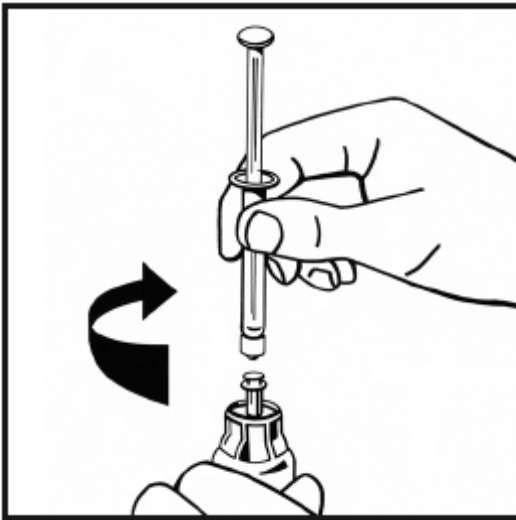
6. Peel back the paper cover from the pre-filled syringe package. Hold the plunger rod at the end and do not touch the shaft. Attach the threaded end of the plunger rod to the solvent syringe plunger. Turn the plunger rod clockwise until a slight resistance is felt.



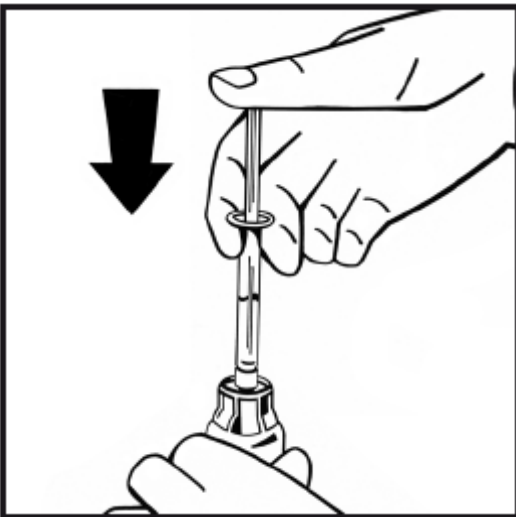
7. Break off the tamper-proof plastic tip from the solvent syringe by snapping the perforation of the cap. Do not touch the inside of the cap or the syringe tip. In case the solution is not used immediately close the filled syringe with the tamper-proof plastic tip for storage.



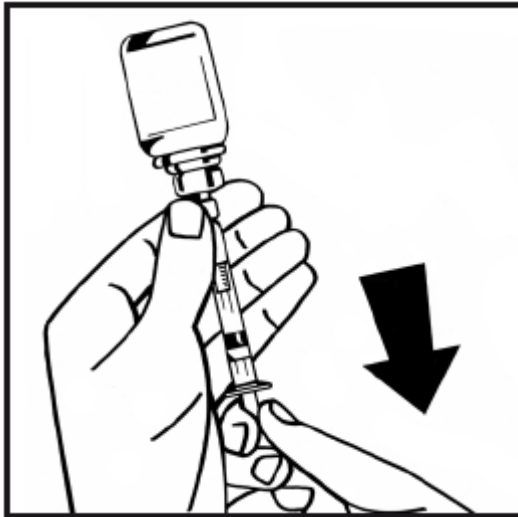
8. Remove the adapter packaging and discard.
9. Firmly connect the solvent syringe to the vial adapter by turning clockwise until resistance is felt.



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
Elersvägen 40
112 75 Stockholm
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/A/14/936/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

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

Octapharma AB
Elersvägen 40
Stockholm
11275
Sweden

Name and address of the manufacturer(s) responsible for batch release

Octapharma AB
Elersvägen 40
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**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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 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.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

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 International Units
Powder and solvent for solution for injection
simoctocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

250 International Units/vial simoctocog alfa (100 IU/ml after reconstitution)

3. LIST OF EXCIPIENTS

Powder: Sucrose, sodium chloride, calcium chloride dihydrate, arginine hydrochloride, sodium citrate dihydrate, poloxamer 188
Solvent: Water for injections
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, 1 vial adapter, 1 butterfly needle, 2 alcohol swabs
1 Powder vial contains 250 International Units simoctocog alfa.
1 Pre-filled syringe contains 2.5 ml water for injections

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 in the original package in order to protect from light.

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
Elersvägen 40
112 75 Stockholm
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/A/14/936/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Nuwiq 250

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
VIAL WITH POWDER FOR SOLUTION FOR INJECTION

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

Nuwiq 250 International Units, 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

250 IU/vial

6. OTHER

Octapharma-Logo

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nuwiq 500 International Units
Powder and solvent for solution for injection
simoctocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

500 International Units/vial simoctocog alfa (200 IU/ml after reconstitution)

3. LIST OF EXCIPIENTS

Powder: Sucrose, sodium chloride, calcium chloride dihydrate, arginine hydrochloride, sodium citrate dihydrate, poloxamer 188
Solvent: Water for injections
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, 1 vial adapter, 1 butterfly needle, 2 alcohol swabs
1 Powder vial contains 500 International Units simoctocog alfa.
1 Pre-filled syringe contains 2.5 ml water for injections

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 in the original package in order to protect from light.

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
Elersvägen 40
112 75 Stockholm
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/A/14/936/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Nuwiq 500

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
VIAL WITH POWDER FOR SOLUTION FOR INJECTION

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

Nuwiq 500 International Units, 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

500 IU/vial

6. OTHER

Octapharma-Logo

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nuwiq 1000 International Units
Powder and solvent for solution for injection
simoctocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1000 International Units/vial simoctocog alfa (400 IU/ml after reconstitution)

3. LIST OF EXCIPIENTS

Powder: Sucrose, sodium chloride, calcium chloride dihydrate, arginine hydrochloride, sodium citrate dihydrate, poloxamer 188
Solvent: Water for injections
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, 1 vial adapter, 1 butterfly needle, 2 alcohol swabs
1 Powder vial contains 1000 International Units simoctocog alfa.
1 Pre-filled syringe contains 2.5 ml water for injections

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 in the original package in order to protect from light.

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
Elersvägen 40
112 75 Stockholm
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/A/14/936/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Nuwiq 1000

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
VIAL WITH POWDER FOR SOLUTION FOR INJECTION

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

Nuwiq 1000 International Units, 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

1000 IU/vial

6. OTHER

Octapharma-Logo

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nuwiq 2000 International Units
Powder and solvent for solution for injection
simoctocog alfa (recombinant human coagulation factor VIII)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

2000 International Units/vial simoctocog alfa (800 IU/ml after reconstitution)

3. LIST OF EXCIPIENTS

Powder: Sucrose, sodium chloride, calcium chloride dihydrate, arginine hydrochloride, sodium citrate dihydrate, poloxamer 188
Solvent: Water for injections
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, 1 vial adapter, 1 butterfly needle, 2 alcohol swabs
1 Powder vial contains 2000 International Units simoctocog alfa.
1 Pre-filled syringe contains 2.5 ml water for injections

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 in the original package in order to protect from light.

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
Elersvägen 40
112 75 Stockholm
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/A/14/936/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Nuwiq 2000

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
VIAL WITH POWDER FOR SOLUTION FOR INJECTION

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

Nuwiq 2000 International Units, 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

2000 IU/vial

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 Simoctocog alfa (recombinant human coagulation factor VIII)

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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 or pharmacist.
- 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 or pharmacist. 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
2. What you need to know before you use Nuwiq
3. How to use Nuwiq
4. Possible side effects
5. How to store Nuwiq
6. Contents of the pack and other information

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 or pharmacist 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.

If your bleeding is not controlled with Nuwiq, tell your doctor immediately. You may have developed ‘factor VIII inhibitors’ and your doctor may wish to carry out tests to confirm this. Factor VIII inhibitors are antibodies in the blood that block the factor VIII you are using. This makes factor VIII less effective in controlling bleeding. You should tell your doctor if you have been previously treated

with factor VIII products, especially if you developed inhibitors, since there might be a higher risk that it happens again.

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

Other medicines and Nuwiq

Tell your doctor or pharmacist 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 less than 1 mmol sodium (23 mg) per vial.

However depending on your body weight and your dose of Nuwiq, you could receive more than one vial. This should be taken into consideration if you are on a controlled sodium diet.

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

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

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 or pharmacist.

If you stop using Nuwiq

Do not stop using Nuwiq without consulting your doctor or pharmacist.

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

4. Possible side effects

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

Allergic reactions

You should be aware of the early signs of allergic reactions. If severe, sudden allergic reactions (anaphylactic) occur (very rare, up to 1 in 10,000), the injection must be stopped immediately. You must contact your doctor immediately if you notice any of the following symptoms:

- rash, hives, wheals, generalised itching,
- swelling of lips and tongue,
- difficulty in breathing, wheezing, tightness in the chest,
- general feeling of being unwell,
- dizziness and loss of consciousness.

These symptoms can be early symptoms of an anaphylactic shock. If any of these symptoms occur, stop the injection immediately and contact your doctor. Severe symptoms require prompt emergency treatment.

Uncommon side effects may affect up to 1 in 100 people

Tingling or numbness (paraesthesia), headache, injection site inflammation, injection site pain, back pain, vertigo, dry mouth.

Side effects related to central venous access devices (CVAD):

catheter-related infection, general (systemic) infection and local blood clot at the catheter site.

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

Use the reconstituted solution immediately after reconstitution.

Warnings against certain visible signs of deterioration

Do not use the product 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 IU of simoctocog alfa.
- The other ingredients are sucrose, sodium chloride, calcium chloride dihydrate, arginine hydrochloride, sodium citrate dihydrate and poloxamer 188

Solvent:

Water for injections

What Nuwiq looks like and contents of the pack

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

Each pack of Nuwiq 250 IU contains:

- 1 powder vial with 250 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

Octapharma AB, Elersvägen 40, 112 75 Stockholm, Sweden

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

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

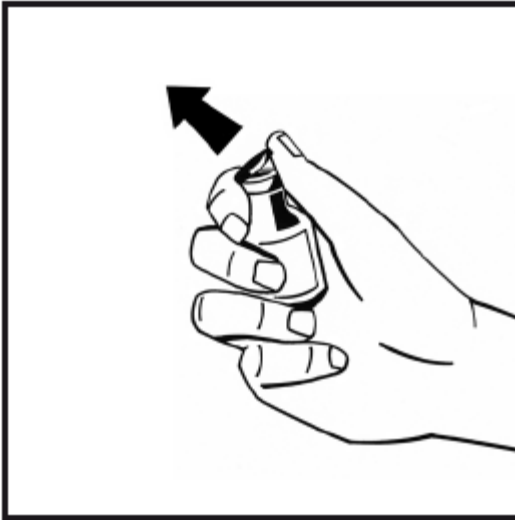
The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case.

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.

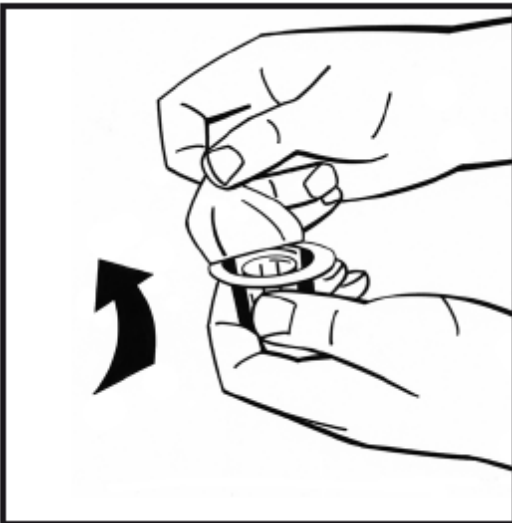
Degree of haemorrhage/ Type of surgical procedure	Factor VIII level required (%) (IU/dL)	Frequency of doses (hours)/ Duration of therapy (days)
<u>Haemorrhage</u>		
Early haemarthrosis, muscle bleeding or oral bleeding	20–40	Repeat every 12 to 24 hours. At least 1 day, until the bleeding episode as indicated 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.
<u>Surgery</u>		
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

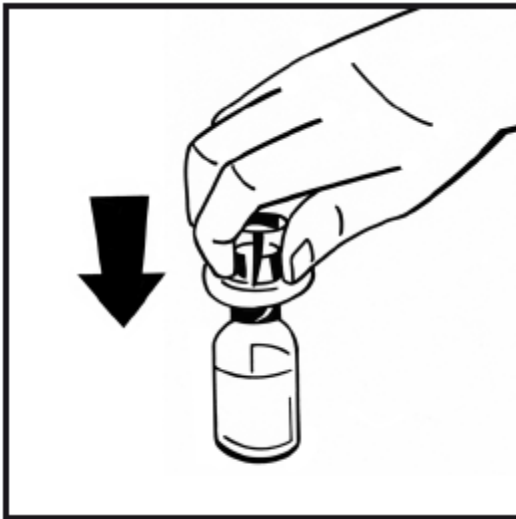
1. Allow the solvent syringe (water for injections) and the powder in the closed vial to reach room temperature. You can do this by holding them in your hands until they feel as warm as your hands. Do not use any other way to heat the vial and pre-filled syringe. This temperature should be maintained during reconstitution.
2. Remove the plastic flip-top 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.



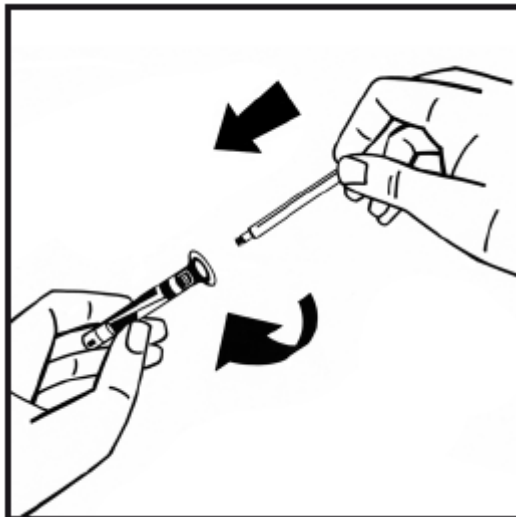
3. Wipe the top of the vial with an alcohol swab. Allow the alcohol to dry.
4. Peel back the paper cover from the vial adapter package. Do not remove the adapter from the package.



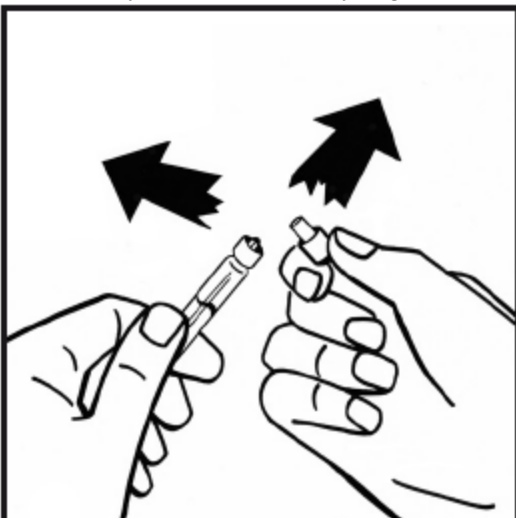
5. Place the powder vial on an even surface and hold it. Take the adapter package and place the vial adapter over the centre of the rubber stopper of the powder vial. Press down firmly the adapter package until the adapter spike penetrates the rubber stopper. The adapter snaps to the vial when done.



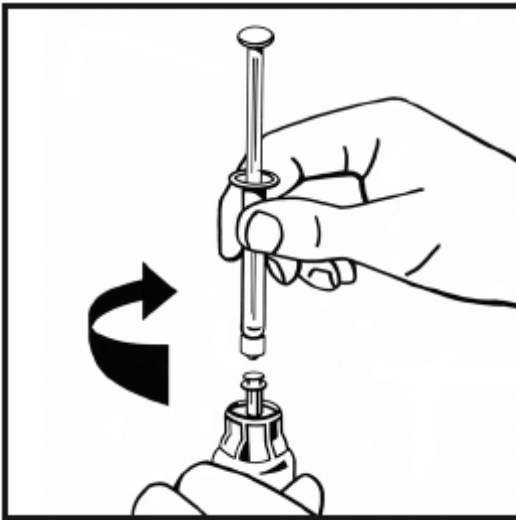
6. Peel back the paper cover from the pre-filled syringe package. Hold the plunger rod at the end and do not touch the shaft. Attach the threaded end of the plunger rod to the solvent syringe plunger. Turn the plunger rod clockwise until a slight resistance is felt.



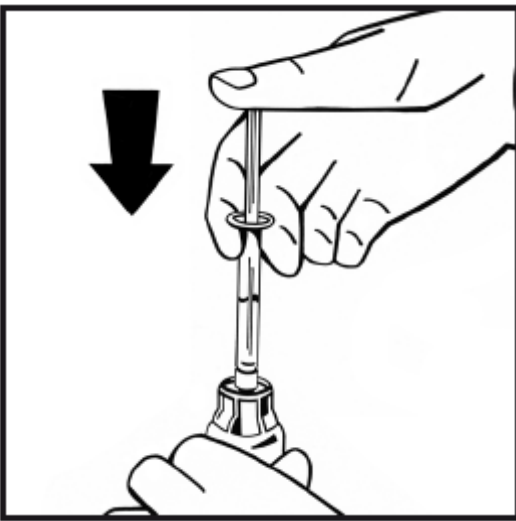
7. Break off the tamper-proof plastic tip from the solvent syringe by snapping the perforation of the cap. Do not touch the inside of the cap or the syringe tip. In case the solution is not used immediately close the filled syringe with the tamper-proof plastic tip for storage.



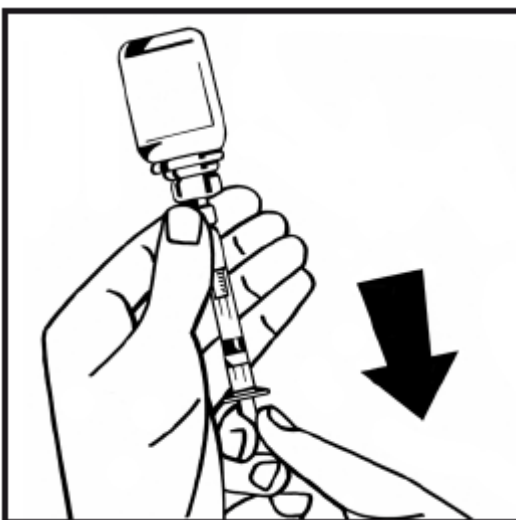
8. Remove the adapter packaging and discard.
9. Firmly connect the solvent syringe to the vial adapter by turning clockwise until resistance is felt.



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.

Package leaflet: Information for the user

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

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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 or pharmacist.
- 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 or pharmacist. 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
2. What you need to know before you use Nuwiq
3. How to use Nuwiq
4. Possible side effects
5. How to store Nuwiq
6. Contents of the pack and other information

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 or pharmacist 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.

If your bleeding is not controlled with Nuwiq, tell your doctor immediately. You may have developed ‘factor VIII inhibitors’ and your doctor may wish to carry out tests to confirm this. Factor VIII inhibitors are antibodies in the blood that block the factor VIII you are using. This makes factor VIII less effective in controlling bleeding. You should tell your doctor if you have been previously treated

with factor VIII products, especially if you developed inhibitors, since there might be a higher risk that it happens again.

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

Other medicines and Nuwiq

Tell your doctor or pharmacist 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 less than 1 mmol sodium (23 mg) per vial.

However depending on your body weight and your dose of Nuwiq, you could receive more than one vial. This should be taken into consideration if you are on a controlled sodium diet.

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

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

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 or pharmacist.

If you stop using Nuwiq

Do not stop using Nuwiq without consulting your doctor or pharmacist.

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

4. Possible side effects

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

Allergic reactions

You should be aware of the early signs of allergic reactions. If severe, sudden allergic reactions (anaphylactic) occur (very rare, up to 1 in 10,000), the injection must be stopped immediately. You must contact your doctor immediately if you notice any of the following symptoms:

- rash, hives, wheals, generalised itching,
- swelling of lips and tongue,
- difficulty in breathing, wheezing, tightness in the chest,
- general feeling of being unwell,
- dizziness and loss of consciousness.

These symptoms can be early symptoms of an anaphylactic shock. If any of these symptoms occur, stop the injection immediately and contact your doctor. Severe symptoms require prompt emergency treatment.

Uncommon side effects may affect up to 1 in 100 people

Tingling or numbness (paraesthesia), headache, injection site inflammation, injection site pain, back pain, vertigo, dry mouth.

Side effects related to central venous access devices (CVAD):

catheter-related infection, general (systemic) infection and local blood clot at the catheter site.

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

Use the reconstituted solution immediately after reconstitution.

Warnings against certain visible signs of deterioration

Do not use the product 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 500 IU of simoctocog alfa.
- The other ingredients are sucrose, sodium chloride, calcium chloride dihydrate, arginine hydrochloride, sodium citrate dihydrate and poloxamer 188

Solvent:

Water for injections

What Nuwiq looks like and contents of the pack

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

Each pack of Nuwiq 500 IU contains:

- 1 powder vial with 500 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

Octapharma AB, Elersvägen 40, 112 75 Stockholm, Sweden

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

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

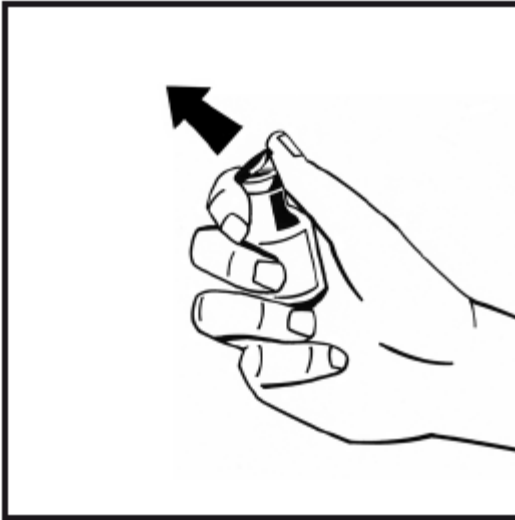
The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case.

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.

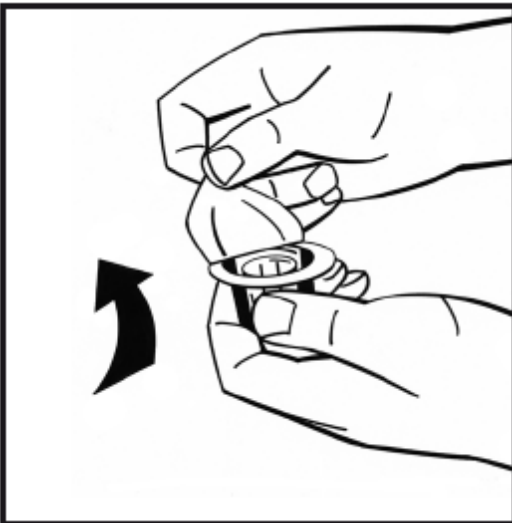
Degree of haemorrhage/ Type of surgical procedure	Factor VIII level required (%) (IU/dL)	Frequency of doses (hours)/ Duration of therapy (days)
<u>Haemorrhage</u>		
Early haemarthrosis, muscle bleeding or oral bleeding	20–40	Repeat every 12 to 24 hours. At least 1 day, until the bleeding episode as indicated 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.
<u>Surgery</u>		
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

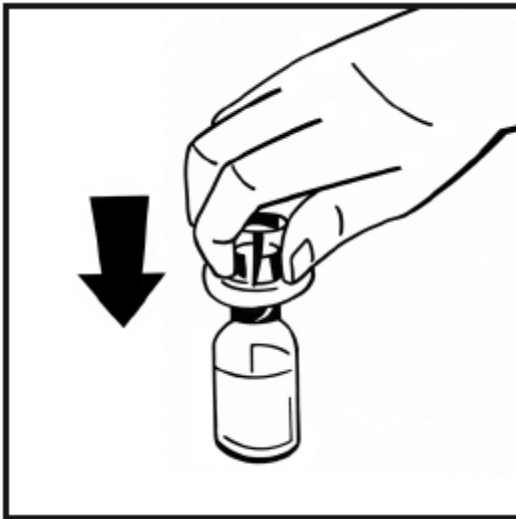
1. Allow the solvent syringe (water for injections) and the powder in the closed vial to reach room temperature. You can do this by holding them in your hands until they feel as warm as your hands. Do not use any other way to heat the vial and pre-filled syringe. This temperature should be maintained during reconstitution.
2. Remove the plastic flip-top 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.



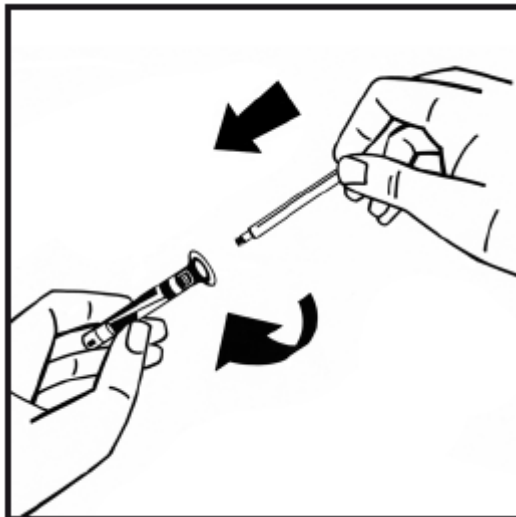
3. Wipe the top of the vial with an alcohol swab. Allow the alcohol to dry.
4. Peel back the paper cover from the vial adapter package. Do not remove the adapter from the package.



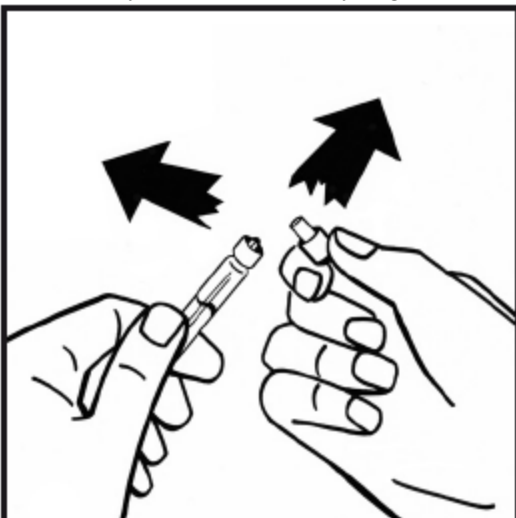
5. Place the powder vial on an even surface and hold it. Take the adapter package and place the vial adapter over the centre of the rubber stopper of the powder vial. Press down firmly the adapter package until the adapter spike penetrates the rubber stopper. The adapter snaps to the vial when done.



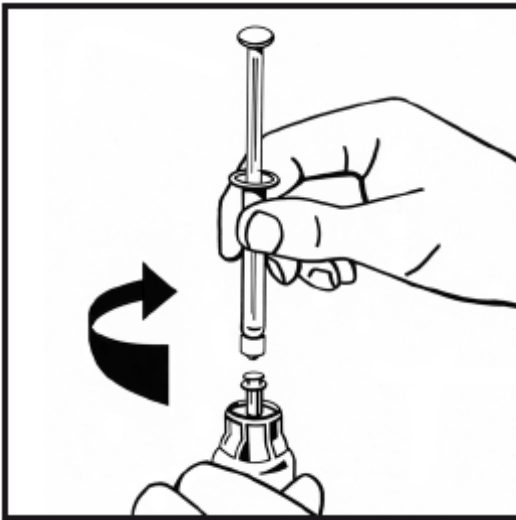
6. Peel back the paper cover from the pre-filled syringe package. Hold the plunger rod at the end and do not touch the shaft. Attach the threaded end of the plunger rod to the solvent syringe plunger. Turn the plunger rod clockwise until a slight resistance is felt.



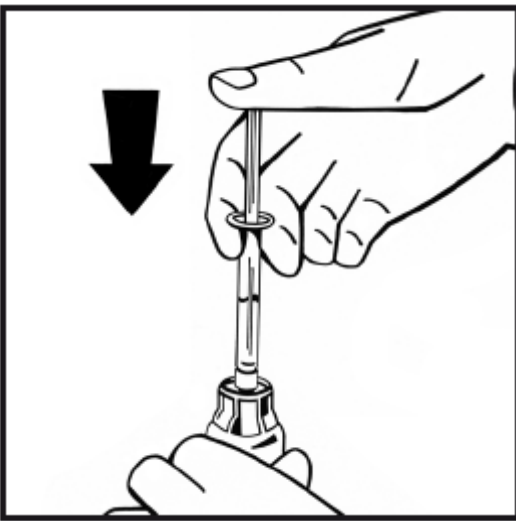
7. Break off the tamper-proof plastic tip from the solvent syringe by snapping the perforation of the cap. Do not touch the inside of the cap or the syringe tip. In case the solution is not used immediately close the filled syringe with the tamper-proof plastic tip for storage.



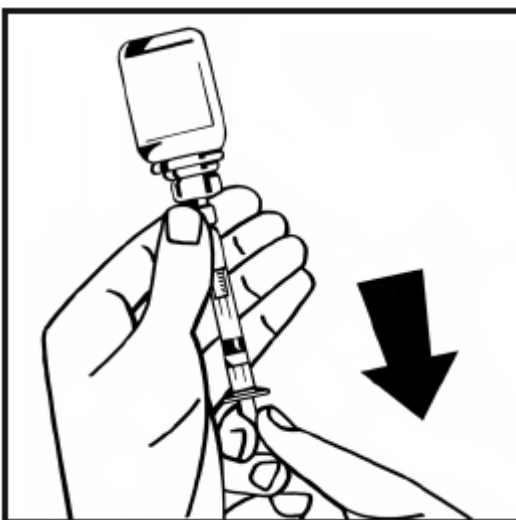
8. Remove the adapter packaging and discard.
9. Firmly connect the solvent syringe to the vial adapter by turning clockwise until resistance is felt.



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.

Package leaflet: Information for the user

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

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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 or pharmacist.
- 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 or pharmacist. 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
2. What you need to know before you use Nuwiq
3. How to use Nuwiq
4. Possible side effects
5. How to store Nuwiq
6. Contents of the pack and other information

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 or pharmacist 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.

If your bleeding is not controlled with Nuwiq, tell your doctor immediately. You may have developed ‘factor VIII inhibitors’ and your doctor may wish to carry out tests to confirm this. Factor VIII inhibitors are antibodies in the blood that block the factor VIII you are using. This makes factor VIII less effective in controlling bleeding. You should tell your doctor if you have been previously treated

with factor VIII products, especially if you developed inhibitors, since there might be a higher risk that it happens again.

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

Other medicines and Nuwiq

Tell your doctor or pharmacist 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 less than 1 mmol sodium (23 mg) per vial.

However depending on your body weight and your dose of Nuwiq, you could receive more than one vial. This should be taken into consideration if you are on a controlled sodium diet.

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

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

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 or pharmacist.

If you stop using Nuwiq

Do not stop using Nuwiq without consulting your doctor or pharmacist.

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

4. Possible side effects

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

Allergic reactions

You should be aware of the early signs of allergic reactions. If severe, sudden allergic reactions (anaphylactic) occur (very rare, up to 1 in 10,000), the injection must be stopped immediately. You must contact your doctor immediately if you notice any of the following symptoms:

- rash, hives, wheals, generalised itching,
- swelling of lips and tongue,
- difficulty in breathing, wheezing, tightness in the chest,
- general feeling of being unwell,
- dizziness and loss of consciousness.

These symptoms can be early symptoms of an anaphylactic shock. If any of these symptoms occur, stop the injection immediately and contact your doctor. Severe symptoms require prompt emergency treatment.

Uncommon side effects may affect up to 1 in 100 people

Tingling or numbness (paraesthesia), headache, injection site inflammation, injection site pain, back pain, vertigo, dry mouth.

Side effects related to central venous access devices (CVAD):

catheter-related infection, general (systemic) infection and local blood clot at the catheter site.

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

Use the reconstituted solution immediately after reconstitution.

Warnings against certain visible signs of deterioration

Do not use the product 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 1000 IU of simoctocog alfa.
- The other ingredients are sucrose, sodium chloride, calcium chloride dihydrate, arginine hydrochloride, sodium citrate dihydrate and poloxamer 188

Solvent:

Water for injections

What Nuwiq looks like and contents of the pack

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

Each pack of Nuwiq 1000 IU contains:

- 1 powder vial with 1000 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

Octapharma AB, Elersvägen 40, 112 75 Stockholm, Sweden

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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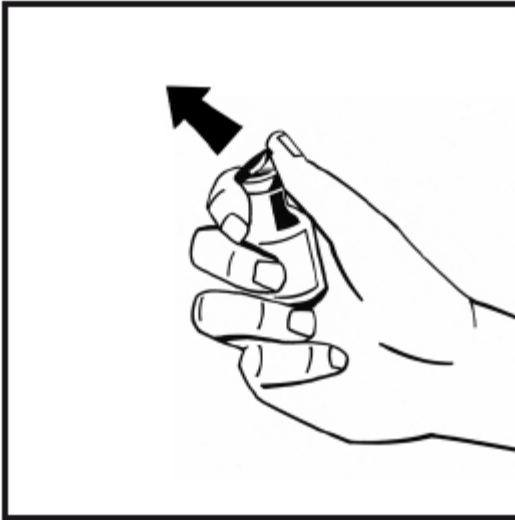
The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case.

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.

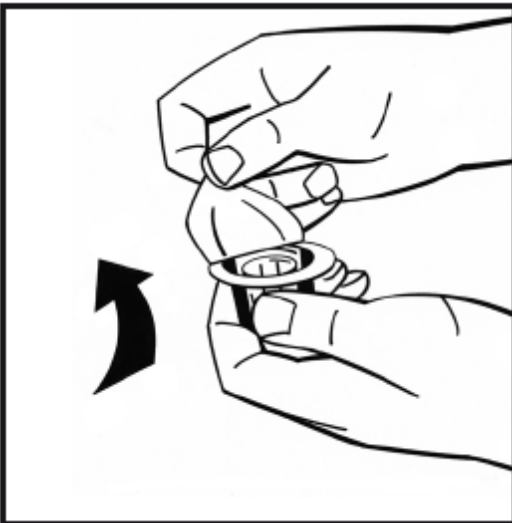
Degree of haemorrhage/ Type of surgical procedure	Factor VIII level required (%) (IU/dL)	Frequency of doses (hours)/ Duration of therapy (days)
<u>Haemorrhage</u>		
Early haemarthrosis, muscle bleeding or oral bleeding	20–40	Repeat every 12 to 24 hours. At least 1 day, until the bleeding episode as indicated 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.
<u>Surgery</u>		
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

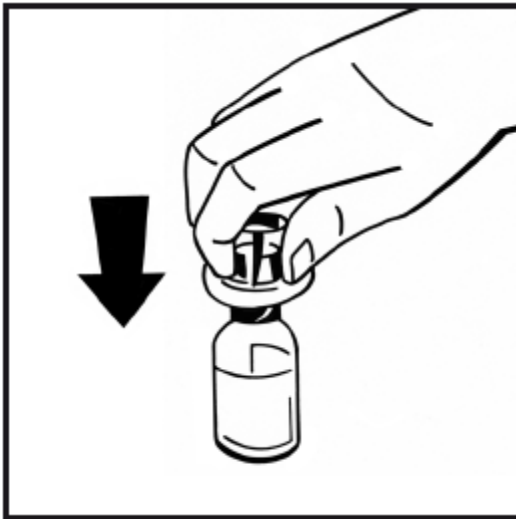
1. Allow the solvent syringe (water for injections) and the powder in the closed vial to reach room temperature. You can do this by holding them in your hands until they feel as warm as your hands. Do not use any other way to heat the vial and pre-filled syringe. This temperature should be maintained during reconstitution.
2. Remove the plastic flip-top 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.



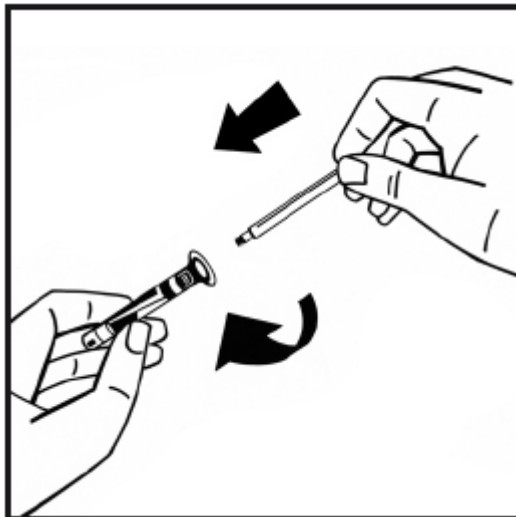
3. Wipe the top of the vial with an alcohol swab. Allow the alcohol to dry.
4. Peel back the paper cover from the vial adapter package. Do not remove the adapter from the package.



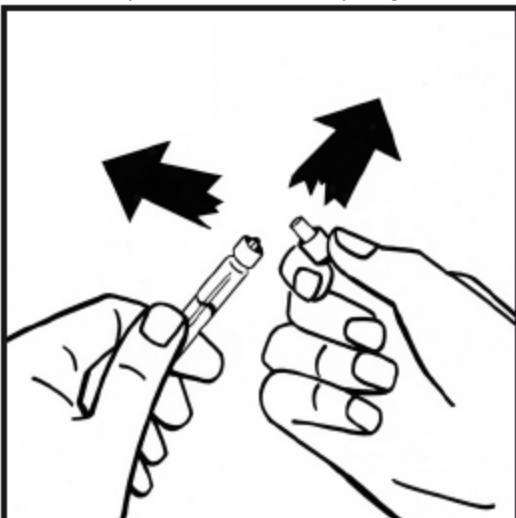
5. Place the powder vial on an even surface and hold it. Take the adapter package and place the vial adapter over the centre of the rubber stopper of the powder vial. Press down firmly the adapter package until the adapter spike penetrates the rubber stopper. The adapter snaps to the vial when done.



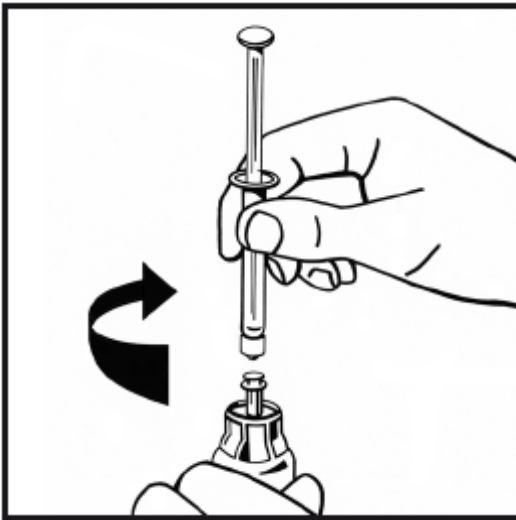
6. Peel back the paper cover from the pre-filled syringe package. Hold the plunger rod at the end and do not touch the shaft. Attach the threaded end of the plunger rod to the solvent syringe plunger. Turn the plunger rod clockwise until a slight resistance is felt.



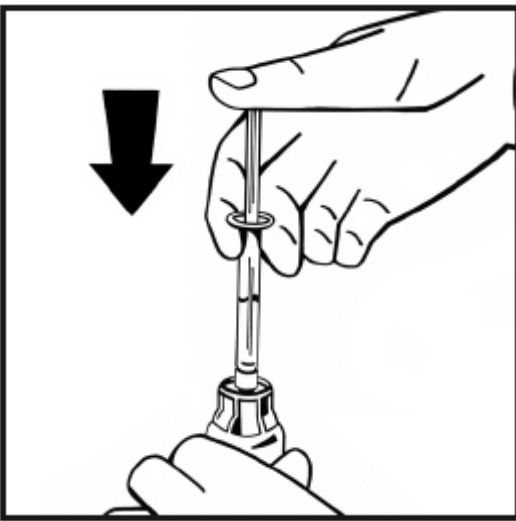
7. Break off the tamper-proof plastic tip from the solvent syringe by snapping the perforation of the cap. Do not touch the inside of the cap or the syringe tip. In case the solution is not used immediately close the filled syringe with the tamper-proof plastic tip for storage.



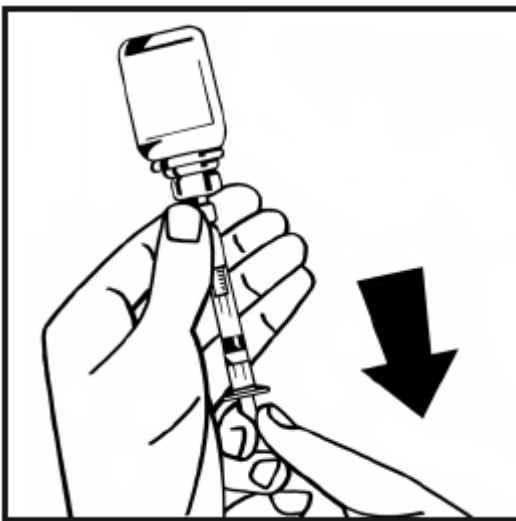
8. Remove the adapter packaging and discard.
9. Firmly connect the solvent syringe to the vial adapter by turning clockwise until resistance is felt.



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.

Package leaflet: Information for the user

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

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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 or pharmacist.
- 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.
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What is in this leaflet

1. What Nuwiq is and what it is used for
2. What you need to know before you use Nuwiq
3. How to use Nuwiq
4. Possible side effects
5. How to store Nuwiq
6. Contents of the pack and other information

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 or pharmacist 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.

If your bleeding is not controlled with Nuwiq, tell your doctor immediately. You may have developed ‘factor VIII inhibitors’ and your doctor may wish to carry out tests to confirm this. Factor VIII inhibitors are antibodies in the blood that block the factor VIII you are using. This makes factor VIII less effective in controlling bleeding. You should tell your doctor if you have been previously treated

with factor VIII products, especially if you developed inhibitors, since there might be a higher risk that it happens again.

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

Other medicines and Nuwiq

Tell your doctor or pharmacist 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 less than 1 mmol sodium (23 mg) per vial.

However depending on your body weight and your dose of Nuwiq, you could receive more than one vial. This should be taken into consideration if you are on a controlled sodium diet.

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.

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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

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

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 or pharmacist.

If you stop using Nuwiq

Do not stop using Nuwiq without consulting your doctor or pharmacist.

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

4. Possible side effects

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

Allergic reactions

You should be aware of the early signs of allergic reactions. If severe, sudden allergic reactions (anaphylactic) occur (very rare, up to 1 in 10,000), the injection must be stopped immediately. You must contact your doctor immediately if you notice any of the following symptoms:

- rash, hives, wheals, generalised itching,
- swelling of lips and tongue,
- difficulty in breathing, wheezing, tightness in the chest,
- general feeling of being unwell,
- dizziness and loss of consciousness.

These symptoms can be early symptoms of an anaphylactic shock. If any of these symptoms occur, stop the injection immediately and contact your doctor. Severe symptoms require prompt emergency treatment.

Uncommon side effects may affect up to 1 in 100 people

Tingling or numbness (paraesthesia), headache, injection site inflammation, injection site pain, back pain, vertigo, dry mouth.

Side effects related to central venous access devices (CVAD):

catheter-related infection, general (systemic) infection and local blood clot at the catheter site.

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

Use the reconstituted solution immediately after reconstitution.

Warnings against certain visible signs of deterioration

Do not use the product 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 2000 IU of simoctocog alfa.
- The other ingredients are sucrose, sodium chloride, calcium chloride dihydrate, arginine hydrochloride, sodium citrate dihydrate and poloxamer 188

Solvent:

Water for injections

What Nuwiq looks like and contents of the pack

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

Each pack of Nuwiq 2000 IU contains:

- 1 powder vial with 2000 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

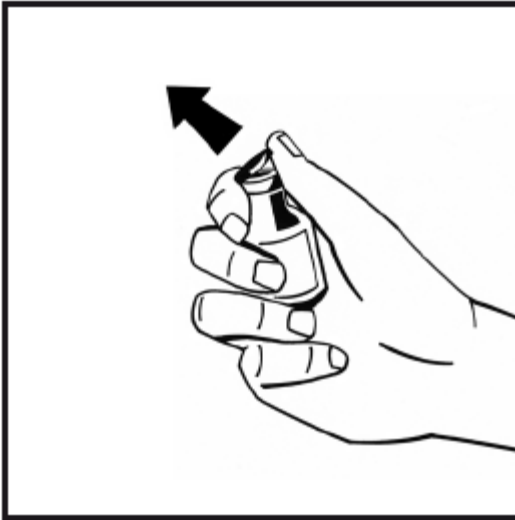
The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case.

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.

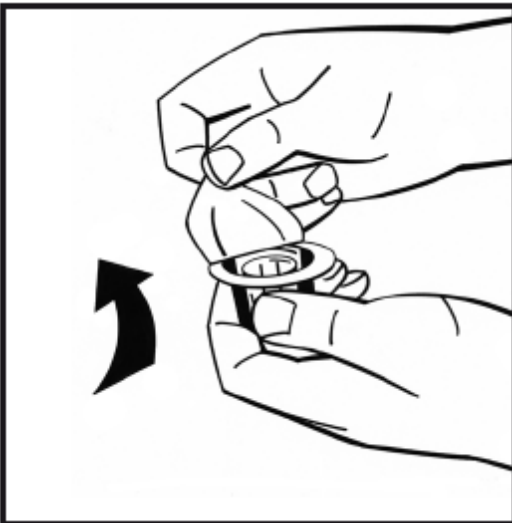
Degree of haemorrhage/ Type of surgical procedure	Factor VIII level required (%) (IU/dL)	Frequency of doses (hours)/ Duration of therapy (days)
<u>Haemorrhage</u>		
Early haemarthrosis, muscle bleeding or oral bleeding	20–40	Repeat every 12 to 24 hours. At least 1 day, until the bleeding episode as indicated 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.
<u>Surgery</u>		
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

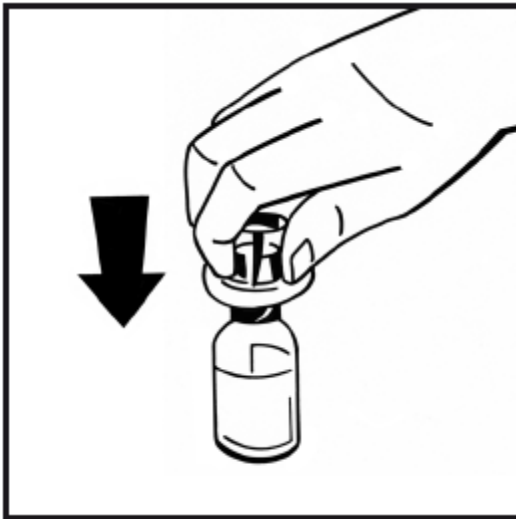
1. Allow the solvent syringe (water for injections) and the powder in the closed vial to reach room temperature. You can do this by holding them in your hands until they feel as warm as your hands. Do not use any other way to heat the vial and pre-filled syringe. This temperature should be maintained during reconstitution.
2. Remove the plastic flip-top 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.



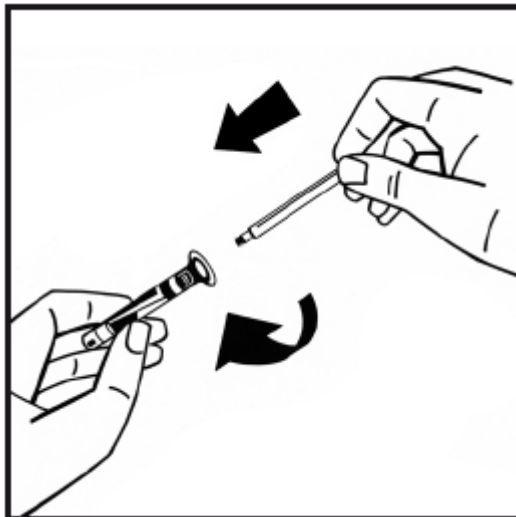
3. Wipe the top of the vial with an alcohol swab. Allow the alcohol to dry.
4. Peel back the paper cover from the vial adapter package. Do not remove the adapter from the package.



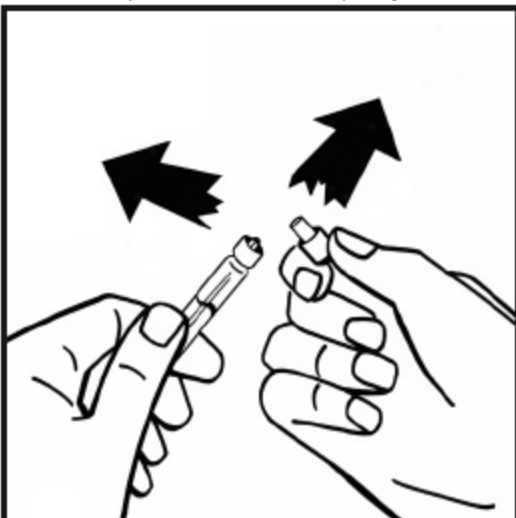
5. Place the powder vial on an even surface and hold it. Take the adapter package and place the vial adapter over the centre of the rubber stopper of the powder vial. Press down firmly the adapter package until the adapter spike penetrates the rubber stopper. The adapter snaps to the vial when done.



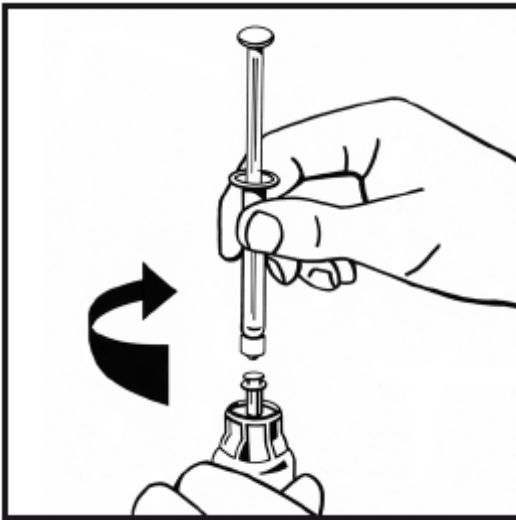
6. Peel back the paper cover from the pre-filled syringe package. Hold the plunger rod at the end and do not touch the shaft. Attach the threaded end of the plunger rod to the solvent syringe plunger. Turn the plunger rod clockwise until a slight resistance is felt.



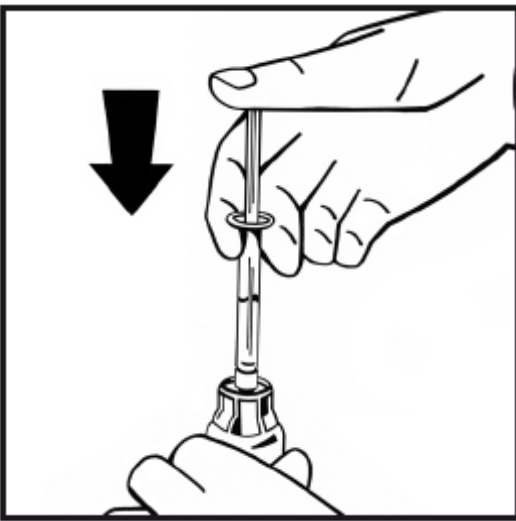
7. Break off the tamper-proof plastic tip from the solvent syringe by snapping the perforation of the cap. Do not touch the inside of the cap or the syringe tip. In case the solution is not used immediately close the filled syringe with the tamper-proof plastic tip for storage.



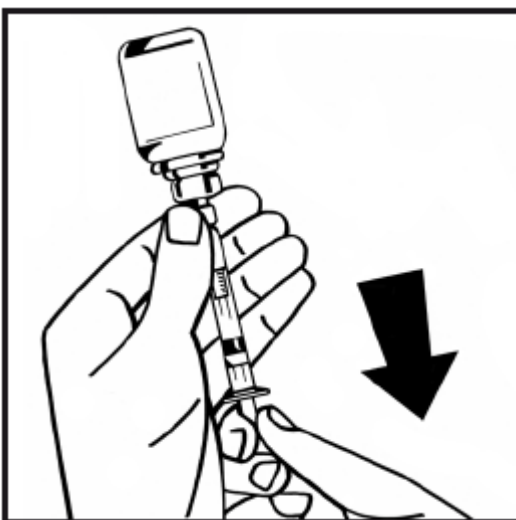
8. Remove the adapter packaging and discard.
9. Firmly connect the solvent syringe to the vial adapter by turning clockwise until resistance is felt.



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.