SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Nuwiq 250 IU powder and solvent for solution for injection.

Nuwiq 500 IU powder and solvent for solution for injection.

Nuwiq 1000 IU powder and solvent for solution for injection.

Nuwiq 2000 IU powder and solvent for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nuwiq 250 IU powder and solvent for solution for injection
Each vial contains nominally 250 IU human coagulation factor VIII (rDNA), simoctocog alfa. Nuwiq 250 IU contains approximately 100 IU/ml of human coagulation factor VIII (rDNA), simoctocog alfa after reconstitution in 2.5 ml.

Nuwiq 500 IU powder and solvent for solution for injection
Each vial contains nominally 500 IU human coagulation factor VIII (rDNA), simoctocog alfa. Nuwiq 500 IU contains approximately 200 IU/ml of human coagulation factor VIII (rDNA), simoctocog alfa after reconstitution in 2.5 ml.

Nuwiq 1000 IU powder and solvent for solution for injection
Each vial contains nominally 1000 IU human coagulation factor VIII (rDNA), simoctocog alfa. Nuwiq 1000 IU contains approximately 400 IU/ml of human coagulation factor VIII (rDNA), simoctocog alfa after reconstitution in 2.5 ml.

Nuwiq 2000 IU powder and solvent for solution for injection
Each vial contains nominally 2000 IU human coagulation factor VIII (rDNA), simoctocog alfa. Nuwiq 2000 IU contains approximately 800 IU/ml of human coagulation factor VIII (rDNA), simoctocog alfa after reconstitution in 2.5 ml.

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: 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.
Nuwiq does not contain Willebrand factor and is not indicated in von Willebrand disease.

4.2 Posology and method of administration

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

Treatment monitoring
During the course of treatment, appropriate determination of factor VIII levels is advised to guide the dose to be administered and the frequency of repeated infusions. Individual patients may vary in their response to factor VIII, demonstrating different half-lives and recoveries. Dose based on bodyweight may require adjustment in underweight or overweight patients. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor VIII activity) is indispensable.

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

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

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

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

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

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

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

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

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

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

Prophylaxis
For long-term prophylaxis against bleeding in patients with severe haemophilia A, the usual doses are 20 to 40 IU of factor VIII per kg body weight at intervals of 2 to 3 days.
In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

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.

Method of administration
Nuwiq is for intravenous use.
It is recommended that not more than 4 ml per minute be administered.

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Hypersensitivity
As with any intravenous protein product, allergic type hypersensitivity reactions are possible. Nuwiq contains traces of human host cell proteins other than factor VIII. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the medicinal product immediately and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.

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

Inhibitors
The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma using the modified assay. The risk of developing inhibitors is correlated to the severity of the disease as well as the exposure to factor VIII, this risk being highest within the first 50 exposure days, but continues throughout life although the risk is uncommon.

The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with low titre posing less of a risk of insufficient clinical response than high titre inhibitors.

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

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

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

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

Development of neutralising antibodies (inhibitors) may occur in patients with haemophilia A treated with factor VIII, including with Nuwiq. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted.

Tabulated list of adverse reactions
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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1. Frequency of adverse drug reactions (ADRs) in clinical trials

MedDRA Standard System Organ Class	Adverse reactions	Frequency
Blood and lymphatic system disorders	Haemorrhagic anaemia Factor VIII inhibition	Uncommon* Uncommon (PTPs) [#] Very common (PUPs)[#]
Immune system disorders	Hypersensitivity	Common*
Nervous system disorders	Paraesthesia 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	Pyrexia Injection site inflammation Injection site pain	Common* Uncommon*

Investigations	Non-neutralising antibody positive (in PTPs)	Uncommon*

* Calculated as patients with ADR per total number of 225 trial patients, of which 135 previously treated patients (PTPs) and 90 previously untreated patients (PUPs).
# Frequency is based on studies with all FVIII products which included patients with severe haemophilia A. PTPs = previously-treated patients, PUPs = previously-untreated patients

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

Paediatric population
Frequency, type and severity of adverse reactions in children 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.

4.9 Overdose

No cases of overdose have been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

The factor VIII/von Willebrand factor complex consists of two molecules (factor VIII and von Willebrand factor) with different physiological functions. When infused into a haemophiliac patient, factor VIII binds to von Willebrand factor in the patient's circulation. Activated factor VIII acts as a cofactor for activated factor IX, accelerating the conversion of factor X to activated factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed. Haemophilia A is a sex-linked hereditary disorder of blood coagulation due to decreased levels of factor VIII:C and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as results of accidental or surgical trauma. By replacement therapy the plasma levels of factor VIII are increased, thereby temporarily enabling a correction of the factor VIII deficiency and correction of the bleeding tendencies.

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

In a clinical study in 32 adult patients with severe haemophilia A, the median consumption of Nuwiq for prophylaxis was 468.7 IU/kg/month. Half of the patients never bled during the prophylactic treatment period (6.0 ± 0.9 months). The mean monthly bleeding rate per patient was 0.095 ± 0.211 for spontaneous bleeds and 0.188 ± 0.307 for all types of bleeds. 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. The median number of infusions required to stop the bleeding was 1.0 (mean ± SD 1.1 ± 0.59). Overall, 60.3% of bleeding episodes were treated with

excellent and 34.1% with good efficacy. Treatment efficacy was judged as moderate in 5.5% of bleeding episodes. Efficacy assessment was missing for one bleeding episode.

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. Of the 59 patients receiving Nuwiq for prophylaxis, 20 (33.9%) patients did not experience any bleeding episode and 14 (23.7%) patients experienced only one bleeding episode during the prophylactic treatment period (6.6 ± 1.4 months). The mean monthly bleeding rate per patient was 0.123 ± 0.272 for spontaneous bleeds and 0.338 ± 0.429 for all types of bleeds. In total 108 bleeding episodes were treated with Nuwiq. The median number of infusions required to stop the bleeding was 1.0 (mean ± SD 2.1 ± 2.95). Overall, 71.3% of bleeding episodes were treated with excellent and 11.1% with good efficacy. Treatment efficacy was judged as moderate in15.7% and as none in 1.9% of bleeding episodes. These data were corroborated by a long-term follow-up of 49 of these children who were treated for an additional median period of approximately 30 months (range from 9.5 to 52 months); during this period 45% of children had no spontaneous bleeds.

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). Surgeries

Efficacy of surgical prophylaxis was assessed in 12 surgeries, 7 in adult and 5 in paediatric patients. Ten surgeries were major and two (both in adults) were minor. Efficacy was rated as “excellent” in all but one surgeries. For one major surgery in adults, efficacy was rated as “moderate”.

A prospective open-label clinical study in PUPs with severe haemophilia A (<1% FVIII:C) is ongoing.

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 haemophilia A (n = 20)

PK parameter	**Chromogenic assay**	**One-stage clotting assay**
	Mean ± SD	**Mean ± SD**
AUC (hr*IU/ml)	22.6 ± 8.0	18.0 ± 5.6
$T_{1/2}$ (hr)	14.7 ± 10.4	17.0 ± 11.8
IVR (%/IU/kg)	2.5 ± 0.4	2.2 ± 0.3
CL (ml/hr/kg)	3.0 ± 1.2	2.9 ± 1.0

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**	**One-stage clotting assay**
	Mean ± SD	**Mean ± SD**
AUC (hr*IU/ml)	13.2 ± 3.4	11.8 ± 2.7
$T_{1/2}$ (hr)	10.0 ± 1.9	13.1 ± 2.6
IVR (%/IU/kg)	1.9 ± 0.4	1.6 ± 0.4
CL (ml/hr/kg)	4.3 ± 1.2	4.1 ± 0.9

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	One-stage clotting assay
	Mean ± SD	Mean ± SD
AUC (hr*IU/ml)	11.7 ± 5.3	10.1 ± 4.6
$T_{1/2}$ (hr)	9.5 ± 3.3	11.9 ± 5.4
IVR (%/IU/kg)	1.9 ± 0.3	1.6 ± 0.2
CL (ml/hr/kg)	5.4 ± 2.4	5.4 ±2.3

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
	One-stage clotting assay Mean ± SD			
AUC (hr*IU/ml)	18.0 ± 5.6	17.2 ± 5.4	19.0 ± 7.5	21.9 ± 3.0
$T_{1/2}$ (hr)	17.0 ± 11.8	17.9 ± 13.8	14.6 ± 6.2	15.6 ± 5.6
IVR (%/IU/kg)	2.2 ± 0.3	2.2 ± 0.3	2.3 ± 0.3	2.2 ± 0.2
CL (ml/hr/kg)	2.9 ± 1.0	3.1 ± 1.0	2.8 ± 0.9	2.2 ± 0.3

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

5.3 Preclinical safety data

In 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

Unopened vial
2 years

During the shelf-life, the product may be kept at room temperature (up to 25°C) for a single period not exceeding 3 months. Once the product has been taken out of the refrigerator the product must not be returned to the refrigerator. Please record the beginning of storage at room temperature on the product carton. Keep the vial in the outer carton in order to protect from light.

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

From a microbiological point of view, the product should be used immediately or within 3 hours 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 at room temperature and storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Each pack contains:

- 1 powder vial with 250, 500, 1000 or 2000 IU simoctocog alfa in a 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 type 1 borosilicate glass syringe
- 1 sterile vial adapter for reconstitution with 1 butterfly needle and 2 alcohol swabs

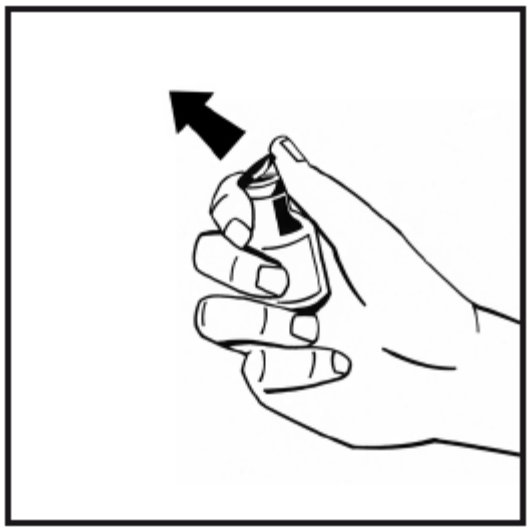
6.6 Special precautions for disposal and other handling

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

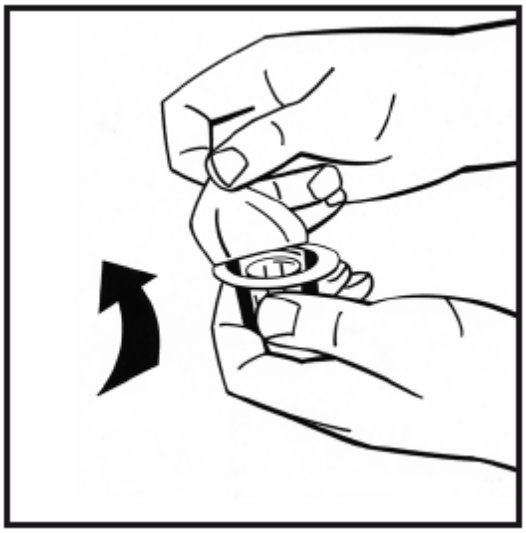
The reconstituted medicinal product should be inspected visually for particulate matter and discoloration prior to administration. The reconstituted medicinal product is a clear, colourless solution, free from foreign particles and has a pH of 6.5 to 7.5. Do not use solutions that are cloudy or have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

Instructions for preparation and administration

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

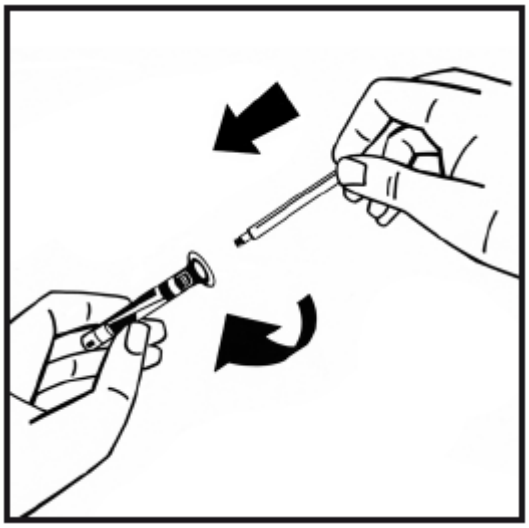


3. Wipe the top of the vial with an alcohol swab. Allow the alcohol to dry.
4. Peel back the paper cover from the vial adapter package. Do not remove the adapter from the package.

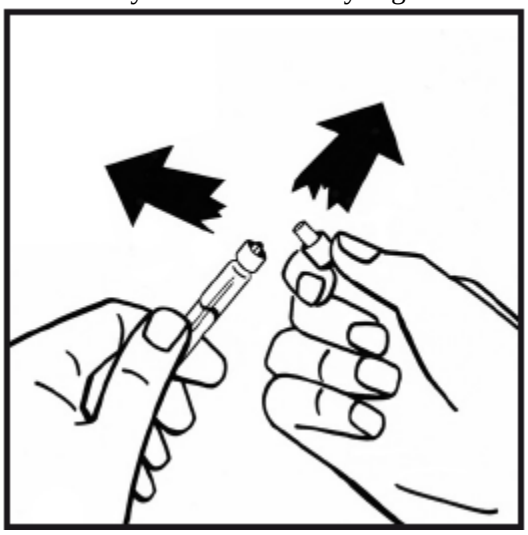


5. Place the powder vial on an even surface and hold it. Take the adapter package and place the vial adapter over the centre of the rubber stopper of the powder vial. Press down firmly the adapter package until the adapter spike penetrates the rubber stopper. The adapter snaps to the vial when done.

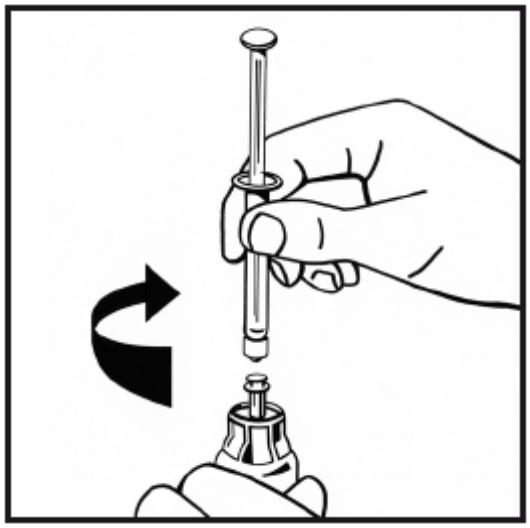
6. Peel back the paper cover from the pre-filled syringe package. Hold the plunger rod at the end and do not touch the shaft. Attach the threaded end of the plunger rod to the solvent syringe plunger. Turn the plunger rod clockwise until a slight resistance is felt.



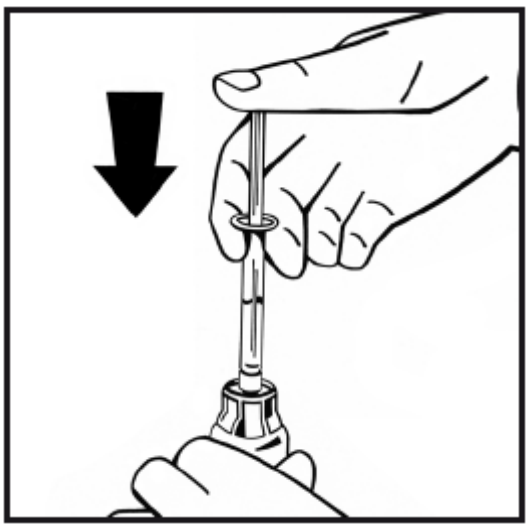
7. Break off the tamper-proof plastic tip from the solvent syringe by snapping the perforation of the cap. Do not touch the inside of the cap or the syringe tip. In case the solution is not used immediately close the filled syringe with the tamper-proof plastic tip for storage.



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

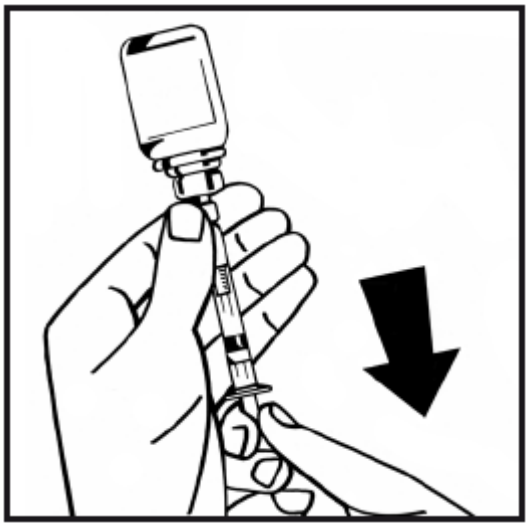


10. Slowly inject all solvent into the powder vial by pressing down the plunger rod.



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.

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

7. MARKETING AUTHORISATION HOLDER

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Singapore 159557

8. MANUFACTURER

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10. DATE OF REVISION OF THE TEXT

2020-03-12