

## **PRODUCT INFORMATION**

### **Nuwiq**

#### **NAME OF THE MEDICINE**

Nuwiq Human cell line recombinant human factor VIII (Human-cl rhFVIII), powder and solvent for solution for injection.

Active ingredient: simoctocog alfa.

CAS number: 1219013-68-9

#### **DESCRIPTION**

Nuwiq contains simoctocog alfa (human coagulation factor VIII (rDNA)) which 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). Human-cl rhFVIII 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. Post-translational modifications of Human-cl rhFVIII are similar to endogenous human coagulation factor VIII of healthy subjects, and thus antigenic carbohydrate epitopes, as described for recombinant factor VIII expressed in hamster cell lines, are not present.

Nuwiq is presented as a powder and solvent for solution for injection. Nuwiq is available in the following presentations:

- Nuwiq 250 containing nominally 250 IU simoctocog alfa per vial. The product contains approximately 100 IU/mL human coagulation factor VIII when reconstituted with 2.5 mL of Water for Injections (WFI).
- Nuwiq 500 containing nominally 500 IU simoctocog alfa per vial. The product contains approximately 200 IU/mL human coagulation factor VIII when reconstituted with 2.5 mL of WFI.
- Nuwiq 1000 containing nominally 1000 IU simoctocog alfa per vial. The product contains approximately 400 IU/mL human coagulation factor VIII when reconstituted with 2.5 mL of WFI.
- Nuwiq 2000 containing nominally 2000 IU simoctocog alfa per vial. The product contains approximately 800 IU/mL human coagulation factor VIII when reconstituted with 2.5 mL of WFI.

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

1 vial of Nuwiq contains the following:

<b>Human-cl rhFVIII</b>	<b>250 IU</b>	<b>500 IU</b>	<b>1000 IU</b>	<b>2000 IU</b>
simoctocog alfa	250 IU	500 IU	1000 IU	2000 IU

Active ingredient: simoctocog alfa

Excipients: sucrose, sodium chloride, calcium chloride, arginine hydrochloride, sodium citrate, poloxamer

## PHARMACOLOGY

### 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 haemophilic 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 (FXa). FXa 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 and results in prolonged 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.

### Pharmacokinetic properties

All pharmacokinetic (PK) studies with Nuwiq were conducted in previously treated patients with severe haemophilia A. The PK results presented in the tables below are derived from cross-over studies of Nuwiq and a full-length recombinant factor VIII product, (Table 1, adolescents and adults) or of Nuwiq and the previously given factor VIII product (Table 2, children 2 to 12 years old), which were all full length plasma-derived or recombinant factor VIII concentrates. The PK (nominal) dose was 50 IU/kg. Plasma samples were analysed in a central laboratory using the chromogenic and the one-stage clotting assay for factor VIII determination.

**Table 1: PK parameters for Nuwiq in adolescent and adult previously treated patients with severe haemophilia A (n = 22)**

PK parameter	Chromogenic assay	One-stage clotting assay
	Mean ± SD	Mean ± SD
AUC (hr*IU/ml)	22.55 ± 7.79	17.95 ± 5.57
AUC <sub>norm</sub> (hr*IU/ml/(IU/kg))	0.39 ± 0.14	0.37 ± 0.11
C <sub>maxnorm</sub> (IU/ml/(IU/kg))	0.025 ± 0.004	0.022 ± 0.003
T <sub>1/2</sub> (hr)	14.73 ± 9.96	17.05 ± 11.23
IVR (%/IU/kg)	2.496 ± 0.369	2.136 ± 0.270
MRT (hr)	19.45 ± 12.02	22.47 ± 14.19
CL (ml/hr/kg)	2.94 ± 1.18	2.96 ± 0.97
V <sub>ss</sub> (ml/kg)	49.58 ± 17.27	59.75 ± 19.76

**Attachment 1: Product information for AusPAR Nuwiq simoctocog alfa rhu Octapharma Australia Pty Ltd PM-2013-02226-1-4 Final 7 June 2016. This Product Information was approved at the time this AusPAR was published.**

AUC = Area under the curve (FVIII:C),  $AUC_{norm}$  = AUC divided by the dose,  $C_{max}$  = Maximal plasma concentration, CL = Clearance,  $IVR = FVIII:C = FVIII$  coagulant activity, IVR = Incremental in vivo recovery, MRT = Mean residence time, SD = Standard deviation,  $T_{1/2}$  = Terminal half-life,  $V_{ss}$  = Volume of distribution at steady state.

**Table 2: PK parameters for Nuwiq in previously treated children aged 6 to 12 years with severe haemophilia A (n = 13)**

<b>PK parameter</b>	<b>Chromogenic assay Mean ± SD</b>	<b>One-stage clotting assay Mean ± SD</b>
AUC (hr*IU/ml)	13.15 ± 3.43	11.77 ± 2.72
$AUC_{norm}$ (hr*IU/ml/(IU/kg))	0.25 ± 0.06	0.26 ± 0.06
$C_{maxnorm}$ (IU/ml/(IU/kg))	0.019 ± 0.004	0.017 ± 0.004
$T_{1/2}$ (hr)	9.99 ± 1.88	13.08 ± 2.59
IVR (%/IU/kg)	1.881 ± 0.440	1.641 ± 0.377
MRT (hr)	12.74 ± 2.34	16.53 ± 2.87
CL (ml/hr/kg)	4.33 ± 1.21	4.05 ± 0.92
$V_{ss}$ (ml/kg)	54.45 ± 14.80	66.07 ± 15.99

AUC = Area under the curve (FVIII:C),  $AUC_{norm}$  = AUC divided by the dose,  $C_{max}$  = Maximal plasma concentration, CL = Clearance,  $IVR = FVIII:C = FVIII$  coagulant activity, IVR = Incremental in vivo recovery, MRT = Mean residence time, SD = Standard deviation,  $T_{1/2}$  = Terminal half-life,  $V_{ss}$  = Volume of distribution at steady state.

**Table 3: PK parameters for Nuwiq in previously treated children aged 2 to 5 years with severe haemophilia A (n = 13)**

<b>PK parameter</b>	<b>Chromogenic assay Mean ± SD</b>	<b>One-stage clotting assay Mean ± SD</b>
AUC (hr*IU/ml)	11.69 ± 5.30	10.07 ± 4.60
$AUC_{norm}$ (hr*IU/ml/(IU/kg))	0.22 ± 0.10	0.22 ± 0.10
$C_{maxnorm}$ (IU/ml/(IU/kg))	0.019 ± 0.003	0.016 ± 0.002
$T_{1/2}$ (hr)	9.49 ± 3.32	11.91 ± 5.36
IVR (%/IU/kg)	1.871 ± 0.270	1.572 ± 0.167
MRT (hr)	11.92 ± 4.93	15.11 ± 7.35
CL (ml/hr/kg)	5.40 ± 2.37	5.41 ± 2.32
$V_{ss}$ (ml/kg)	55.32 ± 7.09	68.29 ± 10.42

AUC = Area under the curve (FVIII:C),  $AUC_{norm}$  = AUC divided by the dose,  $C_{max}$  = Maximal plasma concentration, CL = Clearance,  $IVR = FVIII:C = FVIII$  coagulant activity, IVR = Incremental in vivo recovery, MRT = Mean residence time, SD = Standard deviation,  $T_{1/2}$  = Terminal half-life,  $V_{ss}$  = Volume of distribution at steady state.

***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.

**CLINICAL TRIALS**

Three pivotal clinical studies with Nuwiq have been conducted in a total of 113 previously treated patients (PTPs). In addition, a supportive study and its extension study were conducted in a single center in Russia in a population of 22 adult PTPs who had been inadequately treated since childhood. These studies provide supportive data mainly for assessment of inhibitor development and perioperative prophylaxis. Doses for prophylaxis in clinical trials were 30–40 IU/kg.

	<b>Study I</b>	<b>Study II</b>	<b>Study III</b>	<b>Study IV/V Supportive studies</b>
<b>Number of patients</b>	22	32	59	22
<b>Population studies</b>	PTPs ( $\geq 150$ ED*) with severe haemophilia A ( $\leq 1\%$ )	PTPs ( $\geq 150$ ED*) with severe haemophilia A ( $\leq 1\%$ )	PTPs ( $\geq 50$ ED*) with severe haemophilia A ( $\leq 1\%$ )	PTPs ( $\geq 150$ ED*) with severe haemophilia A ( $\leq 1\%$ )
<b>Mean age (range)</b>	39.6 (12-65)	37.3 (18-75)	6.1 (2-12)	24.5 (18-62)

<b>Assessments</b>	PK (in comparison to full length rFVIII) Efficacy of on-demand treatment Efficacy of peri-operative prophylaxis Safety Immunogenicity	Efficacy of prophylactic treatment Efficacy of treatment of break-through bleeds Efficacy of peri-operative prophylaxis Safety Immunogenicity	PK (in comparison to full length rFVIII) Efficacy of prophylactic treatment Efficacy of treatment of break-through bleeds Efficacy of peri-operative prophylaxis Safety Immunogenicity	PK (in comparison to full length rFVIII) Efficacy of prophylactic treatment Efficacy of treatment of break-through bleeds Efficacy of peri-operative prophylaxis Safety Immunogenicity
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\* ED = Exposure Days

### Study I

This was a prospective, randomised, actively controlled, open-label cross-over, phase II study in 22 adolescent and adult PTPs with severe haemophilia A who were enrolled from nine study centres in three countries. The study was designed to first evaluate the PK of Nuwiq and a full-length rFVIII in a randomised, cross-over fashion. Then, the efficacy and safety of on-demand home treatment with Nuwiq was evaluated for at least 6 months and at least 50 EDs.

PK: The PK results can be found in Table 1.

Efficacy: A total of 986 bleeding episodes were treated with Nuwiq. Efficacy of treatment was rated as "excellent" in 60.3% , "good" in 34.5% and "moderate" in 5.5% of cases. No treatment efficacy was assessed as "none". The vast majority of bleeding episodes were managed with one (91.4%) or two (5.8%) infusions.

Safety: Patients received a total of 1,207 Nuwiq infusions. There were no related adverse events.

Immunogenicity: No inhibitors were observed.

### Study II

This was a prospective, open-label, multi-centre phase III study performed at eleven study centres in four countries. The primary objective was to determine the efficacy of Nuwiq during prophylactic treatment every other day, in the treatment of bleeding episodes and in surgical prophylaxis for at least 6 months and at least 50 EDs.

Efficacy: Thirty-two patients received Nuwiq as prophylaxis for a mean of  $85.1 \pm 15.4$  EDs and  $6.0 \pm 0.9$  months. The mean  $\pm$  SD prophylactic dose per infusion was  $32.8 \pm 2.8$  IU/kg. Half of the patients never bled, 11 (34.4%) bled once and 5 (16.6%) more than once. The mean monthly bleeding rate per patient was  $0.188 \pm 0.307$  for all types of bleeds. A total of

30 bleeding episodes in 15 patients were treated with Nuwiq. Efficacy of treatment was rated as “excellent” in 71.4% and as “good” in 28.6% of cases. No treatment efficacy was assessed as “moderate” or “none”. The vast majority of bleeding episodes were managed with one (81.5%) or two (7.4%) infusions.

Safety: Patients received a total of 2921 infusions with Nuwiq. Two patients experienced a total of 5 possibly related adverse events. One patient reported injection site pain after the first infusion; the second patient experienced vertigo, dry mouth and paresthesia after the first and injection site inflammation after the 15<sup>th</sup> administration of Nuwiq. All of these 5 AEs were mild, non-serious and fully resolved without requiring any action.

Immunogenicity: No inhibitors were observed.

### **Study III**

PK: The PK results can be found in Table 2 and 3.

Efficacy: Fifty-nine paediatric patients received Nuwiq as prophylaxis for a mean of  $89.8 \pm 22.3$  EDs and  $6.6 \pm 1.4$  months. Thirty-eight (64.4%) patients received prophylaxis every other day and 17 (28.8%) three times per week. For four (6.8%) patients, no clear assignment to either of these treatment subgroups was possible. The number of all bleeding episodes per patient during the study ranged from 0 to 12; 20 (33.9%) patients did not experience any bleeding episode and 14 patients (23.7%) experienced one bleeding episode during the study. The mean monthly bleeding rate per patient was  $0.338 \pm 0.429$  for all types of bleeds. A total of 108 bleeding episodes in 32 patients were treated with Nuwiq. Efficacy of treatment was rated as “excellent” in 71.3% , “good” in 11.1%, “moderate” in 15.7%, and “none” in 1.9% of cases. The majority of bleeding episodes were managed with one (68.6%) or two (12.7%) infusions.

Safety: Patients received a total of 5746 infusions with Nuwiq. Two patients experienced a total of two related adverse events (back pain and headache).

Immunogenicity: No inhibitors were observed.

### **Summary of immunogenicity and peri-operative prophylaxis:**

Inhibitors: No FVIII inhibitors were detected in any of the 135 patients (including patients from study III/IV), 129 of them had been exposed for at least 50 EDs.

Peri-operative prophylaxis: Across the 5 studies, the efficacy of Nuwiq as surgical prophylaxis was assessed in a total of 33 surgical procedures in 19 patients; 20 procedures (in 7 patients) were classed as minor and 13 procedures (in 12 patients) were classed as major (e.g. revision of right total knee, total hip replacement, joint arthroscopy, bilateral ankle joint arthroscopic debridement, cholecystectomy and liver biopsy, port catheter implantations, circumcision, total endoprosthesis left hip, total endoprosthesis (right knee). Overall efficacy assessment criteria included amount of blood loss (compared to what is expected) and the requirement of any additional infusions not originally anticipated for this type of procedure. Efficacy assessments for all surgical procedures are summarised in the table below.

### **Overall Efficacy Assessment for Surgical Prophylaxis According to the Classification of the Procedure Across the Studies**

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<b>Classification of surgery</b>					
<b>Efficacy rating</b>	<b>Study I</b>	<b>Study II</b>	<b>Study III</b>	<b>Study IV</b>	<b>Study V</b>
Any (N)	2	5	5	14	7
Excellent	2	4	5	14	4
Good	–	–	–	–	3
Moderate	–	1	–	–	–
None	–	–	–	–	–
Minor (N)	1	1	0	14	4
Excellent	1	1	–	14	4
Good	–	–	–	–	–
Moderate	–	–	–	–	–
None	–	–	–	–	–
Major (N)	1	4	5	0	3
Excellent	1	3	5	–	–
Good	–	–	–	–	3
Moderate	–	1	–	–	–
None	–	–	–	–	–

## **INDICATIONS**

Treatment and prophylaxis of bleeding (also during and after surgery) in previously treated paediatric ( $\geq 2$  years) and adult patients with haemophilia A (congenital factor VIII deficiency).

Nuwiq does not contain von Willebrand Factor and is thus not indicated to treat von Willebrand's Disease.

## **CONTRAINDICATIONS**

Hypersensitivity to the active substance or to any of the excipients.

## **PRECAUTIONS**

### ***Hypersensitivity***

Since no animal derived materials are added during the manufacturing process or to the final medicinal product, the possibility of allergic reactions to such foreign constituents, e.g. trace amounts of mouse or hamster proteins, does not exist with Nuwiq. However, 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.

In the clinical studies conducted with Nuwiq no hypersensitivity reactions have been detected in adult or paediatric patients so far.

### ***Inhibitors***

The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A and can occur at any age. 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.

In the clinical studies conducted with Nuwiq no inhibitors have been detected in adult or paediatric patients so far.

### ***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.

### ***Excipient related considerations (sodium content)***

This medicinal product contains 0.8 mmol (or 18.4 mg) sodium per vial and this should be taken into consideration when treating patients on a controlled sodium diet.

### ***Paediatric Use***

The listed warnings and precautions apply both to adults and children. No data are available in children below the age of 2 years.

### ***Previously Untreated Patients***

There are no safety or efficacy data in previously untreated patients with haemophilia A.



### ***Elderly Use***

The safety of Nuwiq in elderly patients (aged > 65 years) has not been established in controlled clinical trials.

### ***Renal or Hepatic impairment***

The safety of Nuwiq in patients with renal or hepatic impairment has not been studied in clinical trials.

### ***Race***

There is limited information on the safety of Nuwiq in different racial groups. The population in the clinical trials was almost exclusively Caucasian.

### ***Use in Pregnancy and Lactation (Category B2\*)***

Animal reproduction studies have not been conducted with factor VIII.

Based on the rare occurrence of haemophilia A in women, experience regarding the use of factor VIII during pregnancy and breast feeding is not available. Therefore, factor VIII should be used during pregnancy and lactation only if clearly indicated.

### ***Effects on Fertility***

There are no reproductive toxicity studies with Nuwiq .

### ***Effects on Laboratory Tests***

No interaction studies have been performed with Nuwiq.

### ***Genotoxicity and Carcinogenicity***

Carcinogenicity studies have not been performed with Nuwiq due to the immune response to heterologous proteins in non-human mammalian species.

No studies have been performed on the genotoxic potential of Nuwiq. No genotoxic potential has been reported for any commercially available plasma-derived or recombinant FVIII product.

## **INTERACTIONS WITH OTHER MEDICINES**

No interaction studies have been performed with Nuwiq.

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.

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\* Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

## ADVERSE EFFECTS

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).

The following adverse events have been identified in the clinical trials with Nuwiq. The data presented in Table 4 is according to the MedRA system organ classification and internationally agreed frequencies. Within each frequency grouping, adverse events are presented in order of decreasing seriousness.

**Table 4: Frequency of adverse drug reactions (ADRs) per patient, in clinical trials in 135 previously treated patients with severe haemophilia A**

MedDRA Standard System Organ Class	Uncommon ( >0.1% - <1%)*
Nervous system disorders	Parasthesia Headache
General disorders and administration site conditions	Injection site inflammation Injection site pain
Investigations	Non-neutralising anti factor VIII antibody positive (without inhibitory activity as measured by the modified Bethesda assay)
Musculoskeletal and connective tissue disorders	Back pain
Ear and labyrinth disorders	Vertigo
Gastrointestinal disorders	Dry mouth

\* 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.

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).

Since animal derived proteins are not used during manufacturing and are absent in the final product, the possibility of allergic reactions to such foreign constituents, e.g. trace amounts of mouse or hamster proteins, does not exist with Nuwiq.

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.

Although so far no inhibitors have been observed for Nuwiq in clinical studies, 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.

### **Description of selected adverse reactions**

A non-neutralising anti-Factor VIII antibody was detected in one adult patient (see Table 4). 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**

The frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

### **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after approval 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 directly to Octapharma.

## **DOSAGE AND ADMINISTRATION**

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

### **Dosage**

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 tailored for clinical effectiveness on an individual basis.

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. The provided dose formula assumes for convenience an incremental recovery of 2%/IU/kg although clinical studies with simoctocog alfa revealed a mean incremental recovery of >2%/IU/kg in adults and <2%/IU/kg in children (see Tables 1, 2 and 3).

<b>Degree of haemorrhage/ Type of surgical procedure</b>	<b>Factor VIII level required (%) (IU/dL)</b>	<b>Frequency of doses (hours)/ Duration of therapy (days)</b>
<u>Haemorrhage</u>		
Early haemarthrosis, muscle bleeding or oral bleeding	20–40	10–20 IU/kg, repeat every 12–24 hours. At least one day, until the BE as indicated by pain, is resolved or healing is achieved
More extensive haemarthrosis, muscle bleeding or haematoma	30–60	15–30 IU/kg, repeat infusion every 12–24 hours for 3–4 days or more until pain and acute disability are resolved
Life threatening haemorrhages	60–100	30–50 IU/kg, repeat infusion every 8–24 hours until threat is resolved
<u>Surgery</u>		
Minor surgery including tooth extraction	30–60	15–30 IU/kg every 24 hours, at least one day, until healing is achieved
Major surgery	80–100 (pre- and postoperative)	40–50 IU/kg, repeat infusion every 8–24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a FVIII activity of 30% to 60% (IU/dL)

BE = bleeding episode; FVIII = coagulation factor VIII; IU = international units

### ***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 dosage is the same in adults and children, however, shorter dosage intervals or higher doses may be necessary for children.

The pharmacokinetics, safety and efficacy of Nuwiq in previously treated children below the age of 13 has been established. Data has been obtained in 29 children between 2 and 5 years of age, and 30 children between 6 and 12 years of age. Half-life and recovery are slightly less in children than in adults and clearance is slightly higher (refer to the **PHARMACOLOGY** section). Efficacy in prophylaxis and the treatment of bleeds is comparable between children and adults.

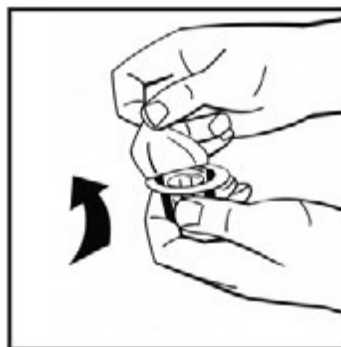
### **Administration**

Nuwiq should be administered via the intravenous route. It is recommended not to administer more than 4 mL per minute.

### ***Instructions for Preparation and Administration***

1. Allow the diluent syringe (water for injections) and the concentrate in the closed vial to reach room temperature. This temperature should be maintained during reconstitution.

2. Remove the plastic flip-top cap from the concentrate vial to expose the central portion of the rubber stopper. Do not remove the grey stopper or metal ring around the top of the vial.

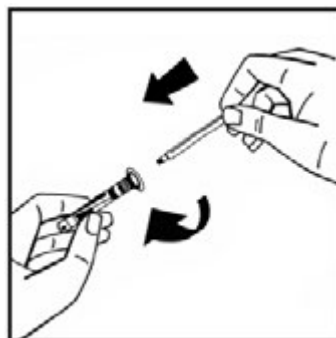


3. Wipe the top of the vial with an alcohol swab. Allow the alcohol to dry.
4. Peel back the paper cover from the vial adapter package. Do not remove the adapter from the package.

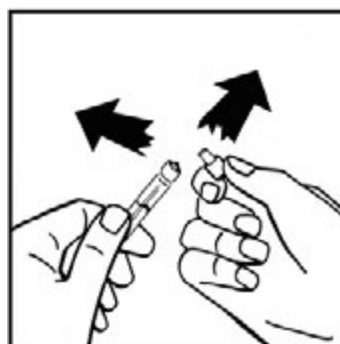
5. Place the concentrate vial on an even surface and hold it. Take the adapter package and place the vial adapter over the centre of the rubber stopper of the concentrate vial. Press down firmly on the adapter package until the adapter spike penetrates the rubber stopper. The adapter snaps to the vial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



6. Peel back the paper cover from the prefilled syringe package. Take the plunger rod at the end and avoid contact with the shaft. Attach the threaded end of the plunger rod to the diluent syringe plunger. Turn the plunger rod clockwise until a slight resistance is felt.

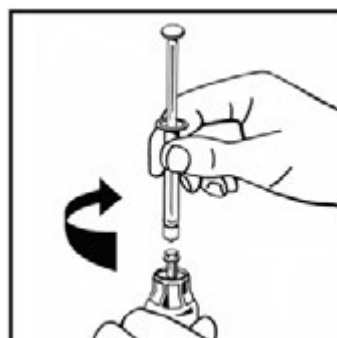


7. Break off the tamper-proof plastic tip from the diluent syringe by snapping the perforation off the cap. Do not touch the inside of the cap or the syringe tip.



8. Remove the adapter package and discard.

9. Firmly connect the diluent syringe to the vial adapter by turning clockwise until resistance is felt.

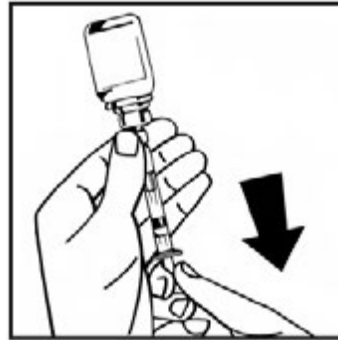


10. Slowly inject all diluent into the concentrate vial by pressing down the plunger rod.



11. Without removing the syringe, dissolve the concentrate powder by gently moving or swirling the vial in circles a few times. **DO NOT SHAKE.** Wait until all the powder dissolves completely.
12. 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 or within 3 hours after reconstitution. In case the solution is not used immediately, close the filled syringe with the tamper-proof plastic tip for storage. Do not refrigerate the solution after reconstitution.
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 concentrate for one treatment, you can follow these pooling steps:

1. Be sure to leave the vial adapter attached to the vial, as you will need it for attaching a larger luer lock syringe
2. Do not detach the diluent syringe or the large luer lock syringe until you are ready to attach the larger luer lock syringe to the next vial (with adapter attached)
3. Remove the diluent syringe from the vial adapter by turning it counter-clockwise until it is completely detached
4. Attach a separate large luer lock syringe by turning clockwise until it is securely attached
5. Slowly pull on the plunger rod to draw the solution into the syringe. Repeat this pooling procedure with each vial you will be using. Once you have pooled the required dose, proceed to administration using the large luer lock syringe. Inject the solution into the vein at a slow speed, not faster than 4 mL per minute.

Do not use after the expiry date given on the label.

The freeze-dried powder should only be reconstituted with the supplied solvent (2.5 mL WFI) using the supplied injection set.

The product is for single use in one patient only. Discard any residue.

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

### ***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.

### **OVERDOSAGE**

No symptoms of overdose have been reported.

### **PRESENTATION AND STORAGE CONDITIONS**

#### ***Pack***

Nuwiq is a white to off-white lyophilised powder for intravenous injection filled in 8 mL colourless type 1 glass vials. The vials are closed with coated bromobutyl stoppers and sealed with aluminium flip-off caps, which have no immediate contact with Nuwiq.

The solvent for reconstitution of Nuwiq, 2.5 mL sterilised WFI, is a clear, colourless liquid provided in prefilled syringes.

Nuwiq is supplied as a combination packaging consisting of:

- one vial of Nuwiq
- one pre-filled WFI syringe
- one vial-adaptor
- one butterfly needle
- two alcohol swabs

Nuwiq is supplied in the following presentations:

- Nuwiq 250 is supplied with 2.5 mL WFI
- Nuwiq 500 is supplied with 2.5 mL WFI
- Nuwiq 1000 is supplied with 2.5 mL WFI
- Nuwiq 2000 is supplied with 2.5 mL WFI

#### ***Storage***

Shelf life is 2 years.

Store at 2°C to 8°C (Refrigerate. Do not freeze).

Keep the vial in the outer carton in order to protect from light. Keep out of reach of children.

The reconstituted solution should be used immediately or within 3 hours after reconstitution.

Keep the reconstituted solution at room temperature. Do not refrigerate.

Do not use after the expiry date given on the label.



**Attachment 1: Product information for AusPAR Nuwiq simoctocog alfa rhu Octapharma Australia Pty Ltd PM-2013-02226-1-4 Final 7 June 2016. This Product Information was approved at the time this AusPAR was published.**

**NAME AND ADDRESS OF SPONSOR**

Octapharma Australia Pty. Ltd.  
Jones Bay Wharf  
42/26-32 Pirrama Road  
Pyrmont NSW 2009  
Australia

**POISON SCHEDULE OF THE MEDICINE**

Exempt from Scheduling, Appendix A of the SUSMP

**DATE OF FIRST INCLUSION ON THE ARTG**

5 November 2014

**DATE OF MOST RECENT AMENDMENT**