ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Voncento 250 IU FVIII / 600 IU VWF (5 ml solvent) powder and solvent for solution for injection/infusion

Voncento 500 IU FVIII /1200 IU VWF (10 ml solvent) powder and solvent for solution for injection/infusion

Voncento 500 IU FVIII / 1200 IU VWF (5 ml solvent) powder and solvent for solution for injection/infusion

Voncento 1000 IU FVIII / 2400 IU VWF (10 ml solvent) powder and solvent for solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Voncento 250 IU FVIII / 600 IU VWF powder and solvent for solution for injection/infusion
One vial of powder contains nominally:
- 250 IU* human coagulation factor VIII** (FVIII).
- 600 IU*** human von Willebrand factor** (VWF).

After reconstitution with the 5 ml water for injections provided, the solution contains 50 IU/ml of FVIII and 120 IU/ml of VWF.

Voncento 500 IU FVIII / 1200 IU VWF powder and solvent for solution for injection/infusion
One vial of powder contains nominally:
- 500 IU* human coagulation factor VIII** (FVIII).
- 1200 IU*** human von Willebrand factor** (VWF).

After reconstitution with the 10 ml water for injections provided, the solution contains 50 IU/ml of FVIII and 120 IU/ml of VWF.

Voncento 500 IU FVIII / 1200 IU VWF powder and solvent for solution for injection/infusion
One vial of powder contains nominally:
- 500 IU* human coagulation factor VIII** (FVIII).
- 1200 IU*** human von Willebrand factor** (VWF).

After reconstitution with the 5 ml water for injections provided, the solution contains 100 IU/ml of FVIII and 240 IU/ml of VWF.

Voncento 1000 IU FVIII / 2400 IU VWF powder and solvent for solution for injection/infusion
One vial of powder contains nominally:
- 1000 IU* human coagulation factor VIII** (FVIII).
- 2400 IU*** human von Willebrand factor** (VWF).

After reconstitution with the 10 ml water for injections provided, the solution contains 100 IU/ml of FVIII and 240 IU/ml of VWF.

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* The FVIII potency (IU) is determined using the European Pharmacopoeia chromogenic assay. The specific FVIII activity of Voncento, prior to the addition of stabiliser, is approximately 70 IU of FVIII/mg protein.
** produced from plasma of human donors
***The VWF activity is determined using the WHO Standard for VWF. The specific VWF activity of Voncento, prior to the addition of stabiliser, is approximately 100 IU of VWF/mg protein.

Excipient with known effect:

Voncento contains approximately 128.2 mmol/l (2.95 mg/ml) of sodium.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection/infusion.
White powder and clear, colourless solvent for solution for injection/infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Voncento can be used for all age groups.

von Willebrand disease (VWD)

Prophylaxis and treatment of haemorrhage or surgical bleeding in patients with VWD, when desmopressin (DDAVP) treatment alone is ineffective or contraindicated.

Haemophilia A (congenital FVIII deficiency)

Prophylaxis and treatment of bleeding in patients with haemophilia A.

4.2 Posology and method of administration

Treatment of VWD and haemophilia A should be supervised by a physician experienced in the treatment of haemostatic disorders.

The decision on the use of the product at home for patients with VWD and with haemophilia A should be made by the treating physician who should ensure that appropriate training is provided and the use is reviewed at intervals.

The ratio between FVIII:C and VWF:RCo in a vial is approximately 1:2.4.

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.

Posology

von Willebrand disease
It is important to calculate the dose using the number of IU of VWF:RCo specified.
Generally, 1 IU/kg VWF:RCo raises the circulating level of VWF:RCo by 0.02 IU/ml (2 %).

Levels of VWF:RCo of > 0.6 IU/ml (60 %) and of FVIII:C of > 0.4 IU/ml (40 %) should be achieved.

On-demand treatment
Usually 40 - 80 IU/kg of von Willebrand factor (VWF:RCo) corresponding to 20 - 40 IU FVIII:C/kg of body weight (BW) are recommended to achieve haemostasis.

An initial dose of 80 IU/kg VWF:RCo may be required, especially in patients with type 3 VWD where maintenance of adequate levels may require greater doses than in other types of VWD.

Prevention of haemorrhage in case of surgery
For prevention of excessive bleeding during or after surgery the application should start 1 - 2 hours before the surgical procedure.

An appropriate dose should be re-administered every 12 - 24 hours. The dose and duration of the treatment depend on the clinical status of the patient, the type and severity of the bleeding, and both VWF:RCo and FVIII:C levels.

When using a FVIII-containing VWF product, the treating physician should be aware that continued treatment may cause an excessive rise in FVIII:C. After 24 - 48 hours of treatment, in order to avoid an excessive rise in FVIII:C, reduced doses and/or prolongation of the dose interval or the use of a VWF product containing a low level of FVIII should be considered (see section 5.2).

Prophylaxis treatment
For long term prophylaxis in patients with VWD, a dose of 25 - 40 IU VWF:RCo /kg body weight should be considered at a frequency of 1 to 3 times per week. In patients with gastrointestinal bleeds or menorrhagia, shorter dose intervals or higher doses may be necessary. The dose and duration of treatment will depend on the clinical status of the patient, as well as their VWF:RCo and FVIII:C plasma levels.

Paediatric VWD population

Treatment of bleeding
Usually 40 - 80 IU/kg of von Willebrand factor (VWF:RCo) corresponding to 20 - 40 IU FVIII:C/kg of body weight (BW) are recommended in paediatric patients to treat a bleed.

Prophylaxis treatment
Patients aged 12 to 18 years old: Dosing is based on the same guidelines as for adults.
Patients aged <12 years old: Based on results from a clinical trial in which paediatric patients under 12 years of age were shown to have lower exposure of VWF, a prophylactic dose range of 40 – 80 IU VWF:RCo/kg body weight 1 to 3 times a week should be considered. (see Section 5.2).
The dose and duration of treatment will depend on the clinical status of the patient, as well as their VWF:RCo and FVIII:C plasma levels.

<u>*Haemophilia A*</u>
It is important to calculate the dose using the number of IU of FVIII:C specified.
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).

1 IU of factorVIII activity is equivalent to that quantity of factor VIII in 1 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 about 2 % of normal activity (*in vivo* recovery 2 IU/dl). The required dose is determined using the following formula:

Required units = body weight [kg] x desired factor VIII rise [% or IU/dl] x 0.5.

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, the factor VIII activity should not fall below the given plasma activity level (in % of normal or IU/dl) within 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 (% or IU/dl)**	**Frequency of doses (hours) / Duration of therapy (days)**
Haemorrhage		
Early haemarthrosis, muscle bleeding or oral bleeding	20 - 40	Repeat infusion every 12 - 24 hours for 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 - 24 hours for 3 - 4 days or more until pain and acute disability are resolved.
Life-threatening haemorrhages	60 - 100	Repeat infusion every 8 - 24 hours until threat is resolved.
Surgery		
Minor surgery including tooth extraction	30 - 60	Repeat infusion every 24 hours for 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 continue therapy for at least another 7 days to maintain a factor VIII activity of 30 % - 60 % (IU/dl).

Prophylaxis treatment
For long term prophylaxis in patients with severe haemophilia A, the usual dose is 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 dose intervals or higher doses may be necessary.

Paediatric haemophilia A population
Dosing in haemophilia A in children and adolescents aged < 18 years old is based on body weight and is therefore generally based on the same guidelines as for adults. In some cases shorter dose intervals or higher doses may be necessary. The frequency of administration should always be oriented to the clinical effectiveness in the individual case.

Currently available data are described in Sections 4.8and 5.2.

Elderly
No dose adjustment is necessary for the older people.

Method of administration

For intravenous use.
For instructions on reconstitution of the medicinal product before administration, see section 6.6. The reconstituted preparation should be injected/infused slowly intravenously at a rate comfortable for the patient.

The injection/infusion rate should not exceed 6 ml per minute. The patient should be observed for any immediate reaction. If any reaction takes place that might be related to the administration of Voncento, the rate of injection should be decreased or the application should be stopped, as required by the clinical condition of the patient (see also section 4.4).

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability
It is strongly recommended that every time that Voncento 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 product.

Hypersensitivity

Allergic type hypersensitivity reactions are possible. 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, the current medical standards for shock treatment should be observed.

Virus safety

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV), and for the non-enveloped hepatitis A virus (HAV).

The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19.

Parvovirus B19 infection may be serious for pregnant women (foetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia).

Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/repeated receipt of human plasma-derived factor VIII/VWF products.

von Willebrand disease

There is a risk of occurrence of thrombotic events, particularly in patients with known clinical or laboratory risk factors. Therefore, patients at risk must be monitored for early signs of thrombosis. Prophylaxis against venous thromboembolism should be instituted, according to the current recommendations.

When using a FVIII-containing VWF product, the treating physician should be aware that continued treatment may cause an excessive rise in FVIII:C. In patients receiving FVIII-containing VWF products, plasma levels of FVIII:C should be monitored to avoid sustained excessive FVIII:C plasma

levels which may increase the risk of thrombotic events, and antithrombotic measures should be considered (see also section 5.2).

Patients with VWD, especially type 3 patients, may develop neutralising antibodies (inhibitors) to VWF. If the expected VWF:RCo activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, an appropriate assay should be performed to determine if a VWF inhibitor is present. In patients with high levels of inhibitor, therapy may not only be ineffective but also lead to anaphylactoid reactions and other therapeutic options should be considered.

Haemophilia A

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 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 FVIII 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, bacteremia and catheter site thrombosis should be considered.

Sodium content

Presentations with 250 IU FVIII / 600 IU VWF (5 ml solvent) and 500 IU FVIII / 1200 VWF IU (5 ml solvent): contain up to 14.75 mg (0.64 mmol) sodium per vial, equivalent to 0.74% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Presentations with 500 IU FVIII / 1200 IU VWF (10 ml solvent) and 1000 IU FVIII / 2400 IU VWF (10 ml solvent): contain up to 29.50 mg (1.28 mmol) sodium per vial, equivalent to 1.48% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Paediatric population

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

4.5 Interaction with other medicinal products and other forms of interaction

No interaction of VWF and FVIII with other medicinal products have been studied.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with Voncento.

von Willebrand disease

Experience in the treatment of pregnant or breast-feeding women is not available. Voncento should be administered to pregnant or breast-feeding VWF deficient women only if clearly indicated, taking into consideration that delivery confers an increased risk of haemorrhagic events in these patients.

Haemophilia A

Based on the rare occurrence of haemophilia A in women, experience regarding the treatment during pregnancy and breastfeeding is not available.
Therefore, Voncento should be used during pregnancy and breast-feeding only if clearly indicated.

Fertility

There are no data on fertility available.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

During treatment with Voncento the following adverse reactions may occur:
Hypersensitivity or allergic reactions, thromboembolic events, pyrexia, headache, dysgeusia and abnormal liver function test levels. Furthermore patients may develop inhibitors to FVIII and VWF.

Tabulated list of adverse reactions

The table presented below is according to the MedDRA system organ classification.

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.

MedDRA Standard System Organ Class	**Adverse Reaction***	**Frequency**
Blood and lymphatic system disorders	FVIII inhibition VWF inhibition	Uncommon (PTPs)** Very common (PUPs)** Not known***
Immune system disorders	Hypersensitivity (including tachycardia, chest pain, chest discomfort and back pain)	Common
Nervous system disorders	Dysgeusia	Uncommon
Vascular disorders	Thromboembolic event	Uncommon
General disorders and administration site conditions	Pyrexia Headache	Common Very common
Investigations	Liver function test abnormal	Uncommon

* Adverse events assessed as related to administration of the Voncento
**Frequency is based on studies with all FVIII products which included patients with severe haemophilia A. PTPs = previously-treated patients, PUPs = previously-untreated patients.
*** Observed during postmarketing surveillance, not observed in clinical trials.

Description of selected adverse reactions

Hypersensitivity (allergic reactions)
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 (including chest pain and chest discomfort), back pain, tingling, vomiting, wheezing) have been observed, and may in some cases progress to severe anaphylaxis (including shock).

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

VWF inhibition
Patients with VWD, especially type 3 patients, may develop neutralising antibodies (inhibitors) to VWF. If such inhibitors occur, the condition will manifest itself as an inadequate clinical response. Such antibodies are precipitating and may occur concomitantly to anaphylactic reactions. Therefore, patients experiencing an anaphylactic reaction should be evaluated for the presence of an inhibitor. In all such cases, it is recommended that a specialised haemophilia centre be contacted.

Thromboembolic events
In patients with VWD, there is a risk of occurrence of thromboembolic events, particularly in patients with known clinical or laboratory risk factors. In patients receiving FVIII-containing VWF products, sustained excessive FVIII:C plasma levels may increase the risk of thromboembolic events (see also section 4.4).

For safety with respect to transmissible agents, see section 4.4.

Paediatric population

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 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

Five cases of overdose have been reported from clinical trials. No adverse reactions have been associated with these reports.

The risk of thromboembolic events cannot be excluded in case of major overdose, especially in patients with VWD.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihaemorrhagics,blood coagulation factors, von Willebrand factor and coagulation factor VIII in combination, ATC code: B02BD06

von Willebrand disease

Exogenously administered human plasma-derived VWF behaves in the same way as endogenous VWF.

Administration of VWF allows correction of the haemostatic abnormalities exhibited by patients who suffer from VWF deficiency (VWD) at two levels:

- VWF re-establishes platelet adhesion to the vascular sub-endothelium at the site of vascular damage (as it binds both to the vascular sub-endothelium and to the platelet membrane), providing primary haemostasis as shown by the shortening of the bleeding time. This effect occurs immediately and is known to depend to a large extent on the level of polymerisation of the protein.
- VWF produces delayed correction of the associated FVIII deficiency. Administered intravenously, VWF binds to endogenous FVIII (which is produced normally by the patient), and by stabilising this factor, avoids its rapid degradation.
  Because of this, administration of pure VWF (VWF product with a low FVIII level) restores the FVIII:C level to normal as a secondary effect after the first infusion with a slight delay.
- Administration of a FVIII:C containing VWF preparation restores the FVIII:C level to normal immediately after the first infusion.

Haemophilia A

Exogenously administered human plasma-derived FVIII behaves in the same way as endogenous FVIII.

The FVIII/VWF complex consists of two molecules (FVIII and VWF) with different physiological functions. When infused into a haemophiliac patient, FVIII binds to VWF in the patient's circulation. Activated FVIII 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 FVIII and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement

therapy the plasma level of FVIII is increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendency.

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

5.2 Pharmacokinetic properties

von Willebrand disease

The pharmacokinetics of Voncento have been evaluated in VWD patients in the non-bleeding state.

Based on a pharmacokinetic study with 12 subjects ≥12 years with VWD, the following pharmacokinetic characteristics for VWF:RCo, VWF:Ag, VWF:CB and FVIII:C were observed:

	VWF:RCo			VWF:Ag			VWF:CB			FVIII:C		
parameter	**N**	**median**	**range**	**N**	**median**	**range**	**N**	**median**	**range**	**N**	**median**	**range**
Incremental recovery (IU/mL)/(IU/kg)	12	0.017	0.012-0.021	12	0.018	0.013-0.022	12	0.022	0.015-0.025	12	0.027	0.016-0.036
Half-life (h)	8	11.53	6.05-35.10	12	18.39	11.41-27.01	12	14.54	9.36-25.10	10	23.65	7.69-57.48
AUC_{0-72} (h*IU/mL)	12	14.46	8.56-37.99	12	33.10	22.65-64.68	12	24.32	14.83-41.14	11	27.85	13.15-66.82
MRT (h)	8	13.25	8.59-25.45	12	24.57	15.28-33.60	12	18.74	11.61-28.57	10	36.57	15.62-85.14
C_{max} (IU/mL)	12	1.48	0.93-3.36	12	2.04	1.52-3.66	12	1.60	1.04-2.66	12	1.00	0.57-1.32
T_{max} (h)	12	0.25	0.25-1.03	12	0.25	0.25-1.00	12	0.25	0.25-1.00	12	1.00	0.25-30.00
C_{min} (IU/mL)	12	0.02	0.00-0.03	12	0.10	0.02-0.17	12	0.05	0.02-0.09	12	0.14	0.03-0.59
Total clearance (mL/(h*kg))	12	6.16	3.06-9.32	12	3.74	2.61-4.78	12	3.20	2.32-4.77	11	1.28	0.62-2.47
V_{ss} (ml/kg)	8	68.3	44.7-158.0	12	74.0	64.5-128.4	12	71.0	47.5-93.7	10	47.5	24.8-72.9

AUC = area under the curve; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; IU = International Unit; MRT = mean residence time; N = number of subjects;t_{max} = time to maximum concentration; V_{ss} = volume of distribution at steady state; VWF:Ag = von Willebrand factor: Antigen; VWF:CB = von Willebrand factor: Collagen Binding; VWF:RCo = von Willebrand factor: Ristocetin Cofactor, FVIII:C = Factor VIII: Coagulant

The relative content of HMW (high molecular weight) VWF multimers in Voncento is on average 86 % when compared to normal human plasma (NHP).

Haemophilia A

The pharmacokinetics of Voncento have been evaluated in haemophilia A patients in the non-bleeding state.

Based on a pharmacokinetic study with 16 subjects ≥ 12 years of age with haemophilia A, the following pharmacokinetic characteristics for FVIII:C were observed:

	FVIII:C		
parameter	**N**	**median**	**range**
Incremental recovery (IU/mL)/(IU/kg)	16	0.021	0.011-0.032
Half-life (h)	16	13.74	8.78-18.51
AUC_{0-48}(h*IU/mL)	16	13.09	7.04-21.79
MRT (h)	16	16.62	11.29-26.31
C_{max} (IU/mL)	16	1.07	0.57-1.57
T_{max} (h)	16	0.50	0.42-4.03
C_{min} (IU/mL)	16	0.06	0.02-0.11
Total clearance(mL/(h*kg)	16	3.82	2.30-7.11
V_{ss} (ml/kg)	16	61.2	35.1-113.1

AUC = area under the curve; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; IU = International Unit; MRT = mean residence time; N = number of subjects; t_{max} = time to maximum concentration; V_{ss} = volume of distribution at steady state; FVIII:C = Factor VIII: Coagulant

Paediatric population

von Willebrand disease

The pharmacokinetic data in patients with von Willebrand disease are very similar to those observed in the adult population.

PK of single dose of 80 IU VWF:RCo/kg body weight was evaluated in paediatric subjects less than 12 years of age with severe VWD (see Table below). Following infusion, peak concentrations of VWF markers (VWF:RCo, VWF:Ag, and VWF:CB) and FVIII:C were achieved immediately with a median IR of 0.012-0.016 (IU/mL)/(IU/kg) for VWF markers and 0.018-0.020 (IU/mL)/(IU/kg) for FVIII:C. The median elimination t1/2 of VWF markers was between 10.00 and 13.48 h whereas FVIII:C had a longer t1/2 between 11.40 and 19.54 h due to a plateau effect that may represent the net effect of decreasing levels of exogenous FVIII, combined with increasing endogenous FVIII levels. PK parameters from the repeat PK evaluation were similar to those from initial PK. Voncento exposure and disposition were comparable between <6-year-old and 6-12-year-old subjects.

Baseline-adjusted initial PK parameters of VWF and FVIII:C in subjects <6 (N=9) and 6-12 years old (N=5)

	VWF:RCo				**VWF:Ag**				**VWF:CB**				**FVIII:C**			
parameter	**N**	**median (range)**	**N**	**median (range)**	**N**	**median (range)**	**N**	**median (range)**	**N**	**median (range)**	**N**	**median (range)**	**N**	**median (range)**	**N**	**median (range)**
	<6 years		**6-12 years**		**<6 years**		**6-12 years**		**<6 years**		**6-12 years**		**<6 years**		**6-12 years**	
Incremental recovery (IU/mL)/(IU/kg)	9	0.012 (0.009-0.017)	5	0.016 (0.009-0.017)	9	0.014 (0.007-0.016)	5	0.015 (0.014-0.022)	9	0.014 (0.009-0.017)	5	0.014 (0.010-0.016)	8	0.018 (0.012-0.048)	5	0.020 (0.008-0.026)
Half-life (h)	5	13.48 (4.13-22.44)	3	11.20 (8.55-11.59)	8	11.15 (7.72-22.36)	5	11.00 (8.61-12.14)	8	10.53 (6.08-15.44)	5	10.00 (7.20-12.11)	4	19.54 (17.96-20.70)	3	11.40 (7.05-32.61)
AUC_{0-72} (h*IU/mL)	9	7.40 (4.26-17.71)	5	10.44 (3.11-15.85)	9	19.41 (11.71-34.55)	5	21.75 (18.72-27.77)	9	15.49 (11.10-25.30)	5	16.46 (12.84-19.63)	8	15.45 (8.25-32.36)	5	19.81 (1.47-34.82)
MRT (h)	5	16.68 (4.36-32.74)	3	12.99 (8.48-13.03)	8	13.31 (9.03-31.68)	5	13.26 (11.06-15.72)	8	12.87 (7.17-20.96)	5	11.70 (9.19-15.22)	4	25.78 (23.87-28.42)	3	15.92 (6.63-44.40)
C_{max} (IU/mL)	9	1.06 (0.69-1.35)	5	1.30 (0.71-1.34)	9	1.66 (1.22-1.92)	5	1.79 (1.44-2.50)	9	1.44 (1.13-1.93)	5	1.28 (1.23-1.83)	8	0.71 (0.46-1.46)	5	0.57 (0.33-0.96)
T_{max} (h)	9	0.55 (0.50-0.62)	5	0.58 (0.50-0.60)	9	0.55 (0.50-0.62)	5	0.58 (0.50-0.60)	9	0.55 (0.50-0.62)	5	0.58 (0.50-0.60)	8	0.58 (0.50-22.52)	5	0.58 (0.50-0.60)
Total clearance (mL/(h*kg)	5	7.30 (2.82-17.32)	3	7.22 (6.14-8.62)	8	5.63 (2.24-13.13)	5	4.93 (4.48-5.10)	8	7.03 (3.66-11.74)	5	6.22 (5.25-7.14)	4	2.46 (1.29-3.87)	3	4.81 (0.96-26.07)
V_{ss} (ml/kg)	5	112.1 (52.3-135.3)	3	80.1 (73.1-93.8)	8	76.8 (70.3-133.5)	5	67.5 (54.6-70.4)	8	84.4 (67.1-113.8)	5	79.7 (54.7-95.9)	4	67.5 (33.1-92.5)	3	76.6 (42.6-172.9)

AUC = area under the curve; C_{max} = maximum plasma concentration; IU = International Unit; MRT = mean residence time; N = number of subjects; t_{max} = time to maximum concentration occurs; V_{ss} = volume of distribution at steady state; VWF:Ag = von Willebrand factor: Antigen; VWF:CB = von Willebrand factor: Collagen Binding; VWF:RCo = von Willebrand factor: Ristocetin Cofactor, FVIII:C = Factor VIII: Coagulant

Haemophilia A

PK of single dose of 50 IU FVIII/kg body weight was evaluated in 31 paediatric subjects less than 12 years of age with Haemophilia A (see Table below). Following infusion, peak concentrations of FVIII:C were achieved immediately with a median IR of approximately 0.016 (IU/mL)/(IU/kg) for FVIII:C. The median elimination $t_{1/2}$ of FVIII:C was approximately 10 h. PK parameters from the repeat PK evaluation were similar to those from initial PK. Voncento exposure and disposition were comparable between <6-year-old and 6-12-year-old subjects.

Baseline-adjusted initial PK parameters of FVIII:C in subjects <6 (N=15) and 6-12 years old (N=16)

	FVIII:C					
parameter	**N**	**median**	**range**	**N**	**median**	**range**
	<6 years			6-12 years		
Incremental recovery (IU/mL)/(IU/kg)	15	0.015	0.009-0.019	16	0.016	0.010-0.026
Half-life (h)	15	9.62	7.75-18.20	16	10.00	8.89-12.50
AUC_{0-48} (h*IU/mL)	15	8.23	3.96-11.04	16	9.90	6.17-17.62
MRT (h)	15	13.51	7.95-17.38	16	13.89	12.11-17.07
C_{max} (IU/mL)	15	0.75	0.46-0.94	16	0.84	0.51-1.21
T_{max} (h)	15	0.58	0.53-0.58	16	0.58	0.50-1.00
Total clearance (mL/(h*kg)	15	6.22	4.22-11.34	16	4.88	2.54-7.74
V_{ss} (ml/kg)	15	75.3	63.8-197.2	16	71.9	42.1-109.3

AUC = area under the curve; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; IU = International Unit; MRT = mean residence time; N = number of subjects; t_{max} = time to maximum concentration; V_{ss} = volume of distribution at steady state; FVIII:C = Factor VIII: Coagulant

5.3 Preclinical safety data

Voncento contains FVIII and VWF as active ingredients which are derived from human plasma and act like endogenous constituents of plasma. Preclinical studies with repeated dose applications (chronic toxicity, carcinogenicity and mutagenicity) cannot be reasonably performed in conventional animal models due to the development of antibodies following the application of heterologous human proteins.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Calcium chloride
Human albumin
Sodium chloride
Sodium citrate
Sucrose
Trometamol

Solvent
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products, diluents or solvents except those mentioned in section 6.1.

6.3 Shelf life

3 years.

Chemical and physical in-use stability has been demonstrated for 8 hours at room temperature (below 25 °C). From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Do not store above 25 °C.

Do not freeze. Keep vials 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

Voncento 250 IU FVIII / 600 IU VWF powder and solvent for solution for injection/infusion
Powder (250 IU/600 IU) in a vial (type I glass), with a stopper (rubber) a disc (plastic) and a cap (aluminium).
5 ml of solvent in a vial (type I glass), with a stopper (rubber) a disc (plastic) and a cap (aluminium).

One pack contains:
1 vial with powder
1 vial with 5 ml water for injections
1 filter transfer device 20/20
One inner box containing:
1 disposable 10 ml syringe
1 venipuncture set
2 alcohol swabs
1 non-sterile plaster

Voncento 500 IU FVIII / 1200 IU VWF powder and solvent for solution for injection/infusion
Powder (500 IU/1200 IU) in a vial (type I glass), with a stopper (rubber) a disc (plastic) and a cap (aluminium).
10 ml of solvent in a vial (type I glass), with a stopper (rubber) a disc (plastic) and a cap (aluminium).

One pack contains:
1 vial with powder
1 vial with 10 ml water for injections
1 filter transfer device 20/20
One inner box containing:
1 disposable 10 ml syringe
1 venipuncture set
2 alcohol swabs
1 non-sterile plaster

Voncento 500 IU FVIII / 1200 IU VWF powder and solvent for solution for injection/infusion
Powder (500 IU/1200 IU) in a vial (type I glass), with a stopper (rubber) a disc (plastic) and a cap (aluminium).
5 ml of solvent in a vial (type I glass), with a stopper (rubber) a disc (plastic) and a cap (aluminium).

One pack contains:
1 vial with powder
1 vial with 5 ml water for injections
1 filter transfer device 20/20
One inner box containing:
1 disposable 10 ml syringe
1 venipuncture set
2 alcohol swabs
1 non-sterile plaster

Voncento 1000 IU FVIII / 2400 IU VWF powder and solvent for solution for injection/infusion
Powder (1000 IU/2400 IU) in a vial (type I glass), with a stopper (rubber) a disc (plastic) and a cap (aluminium).
10 ml of solvent in a vial (type I glass) with a stopper (rubber) a disc (plastic) and a cap (aluminium).

One pack contains:
1 vial with powder
1 vial with 10 ml water for injections
1 filter transfer device 20/20
One inner box containing:
1 disposable 10 ml syringe
1 venipuncture set
2 alcohol swabs
1 non-sterile plaster

Not all pack sizes may be marketed.

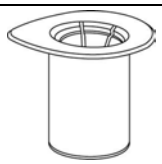
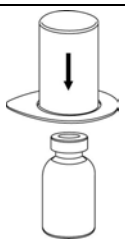
6.6 Special precautions for disposal and other handling

General instructions

The solution should be clear or slightly opalescent. After filtering/withdrawal (see below) the reconstituted product should be inspected visually for particulate matter and discoloration prior to administration. Do not use visibly cloudy solutions or solutions still containing flakes or particles. Reconstitution and withdrawal must be carried out under aseptic conditions.

Reconstitution

Bring the solvent to room temperature. Ensure powder and solvent vial flip caps are removed and the stoppers are treated with an antiseptic solution and allowed to dry prior to opening the Mix2Vial package.

 1	1. Open the Mix2Vial package by peeling off the lid. Do **not** remove the Mix2Vial from the blister package!
 2	2. Place the **solvent vial** on an even, clean surface and hold the vial tight. Take the Mix2Vial together with the blister package and push the spike of the **blue** adapter end **straight down** through the solvent vial stopper.
 3	3. Carefully remove the blister package from the Mix2Vial set by holding at the rim, and pulling **vertically** upwards. Make sure that you only pull away the blister package and not the Mix2Vial set.
 4	4. Place the **product vial** on an even and firm surface. Invert the solvent vial with the Mix2Vial set attached and push the spike of the **transparent** adapter end **straight down** through the product vial stopper. The solvent will automatically flow into the product vial.

 5	5. With one hand grasp the product-side of the Mix2Vial set and with the other hand grasp the solvent-side and unscrew the set carefully counterclockwise into two pieces to avoid excessive build-up of foam when dissolving the product. Discard the solvent vial with the blue Mix2Vial adapter attached.
 6	6. Gently swirl the product vial with the transparent adapter attached until the substance is fully dissolved. Do not shake.
 7	7. Draw air into an empty, sterile syringe. While the product vial is upright, connect the syringe to the Mix2Vial´s Luer Lock fitting by screwing clockwise. Inject air into the product vial.

Withdrawal and application

 8	8. While keeping the syringe plunger pressed, turn the system upside down and draw the solution into the syringe by pulling the plunger back slowly.
 9	9. Now that the solution has been transferred into the syringe, firmly hold on to the barrel of the syringe (keeping the syringe plunger facing down) and disconnect the transparent Mix2Vial adapter from the syringe by unscrewing counterclockwise.

For injection of Voncento only the provided administration sets should be used because treatment failure can occur as a consequence of FVIII adsorption to the internal surfaces of some injection/infusion equipment.

In case large volumes of Voncento are required, it is possible to pool several vials of Voncento via a commercially available infusion set (e.g. a syringe pump for intravenous application of medicinal products). However, in these cases the initially reconstituted solution of Voncento should not be diluted any further.

Administer the solution slowly intravenously (see section 4.2), taking care to ensure that no blood enters the syringe filled with product.

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

7. MARKETING AUTHORISATION HOLDER

CSL Behring GmbH
Emil-von-Behring-Str. 76
35041 Marburg
Germany

8. MARKETING AUTHORIZATION NUMBER(S)

EU/1/13/857/001
EU/1/13/857/002
EU/1/13/857/003
EU/1/13/857/004

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorisation: 12 August 2013
Date of latest renewal: 26 April 2018

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. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURER 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. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substances

CSL Behring AG
Wankdorfstrasse 10
3014 Bern
SWITZERLAND

CSL Behring (Australia) Pty Ltd
189-209 Camp Road
Broadmeadows
Victoria 3047
AUSTRALIA

Name and address of the manufacturer(s) responsible for batch release
CSL Behring GmbH
Emil-von-Behring-Straße 76
35041 Marburg
GERMANY

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).

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

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 six 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
Carton 250 IU/600 IU

1. NAME OF THE MEDICINAL PRODUCT

Voncento 250 IU FVIII / 600 IU VWF (5 ml solvent) powder and solvent for solution for injection/infusion
human coagulation factor VIII/human von Willebrand factor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

human coagulation factor VIII 250 IU
human von Willebrand factor 600 IU

3. LIST OF EXCIPIENTS

Other ingredients: calcium chloride, human albumin, sodium chloride, sodium citrate, sucrose, trometamol. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

powder and solvent for solution for injection/infusion
1 vial with powder
1 vial with 5 ml water for injections
1 filter transfer device 20/20
One inner box containing:
1 disposable 10 ml syringe
1 venipuncture set
2 alcohol swabs
1 non-sterile plaster

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use

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 below 25 °C. Do not freeze.
Keep the vials in the outer carton 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

CSL Behring GmbH, 35041 Marburg, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/857/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Voncento 250 IU / 600 IU

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
Powder vial 250 IU/600 IU

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

Voncento 250 IU FVIII / 600 IU VWF powder for solution for injection/infusion
For IV use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

coagulation factor VIII 250 IU
von Willebrand factor 600 IU

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
Solvent vial label 5 ml

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

Water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
Carton 500 IU/1200 IU

1. NAME OF THE MEDICINAL PRODUCT

Voncento 500 IU FVIII / 1200 IU VWF(10 ml solvent) powder and solvent for solution for injection/infusion
human coagulation factor VIII/human von Willebrand factor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

human coagulation factor VIII 500 IU
human von Willebrand factor 1200 IU

3. LIST OF EXCIPIENTS

Other ingredients: calcium chloride, human albumin, sodium chloride, sodium citrate, sucrose, trometamol. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

powder and solvent for solution for injection/infusion
1 vial with powder
1 vial with 10 ml water for injections
1 filter transfer device 20/20
One inner box containing:
1 disposable 10 ml syringe
1 venipuncture set
2 alcohol swabs
1 non-sterile plaster

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use

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 below 25 °C. Do not freeze.

Keep the vials in the outer carton 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

CSL Behring GmbH, 35041 Marburg, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/857/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Voncento 500 IU / 1200 IU

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
Powder vial 500 IU/1200 IU

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

Voncento 500 IU FVIII /1200 IU VWF powder for solution for injection/infusion
For IV use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

coagulation factor VIII 500 IU
von Willebrand factor 1200 IU

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
Solvent vial label 10 ml

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

Water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
Carton 500 IU/1200 IU

1. NAME OF THE MEDICINAL PRODUCT

Voncento 500 IU FVIII / 1200 IU VWF (5 ml solvent) powder and solvent for solution for injection/infusionhuman coagulation factor VIII/human von Willebrand factor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

human coagulation factor VIII 500 IU
human von Willebrand factor 1200 IU

3. LIST OF EXCIPIENTS

Other ingredients: calcium chloride, human albumin, sodium chloride, sodium citrate, sucrose, trometamol. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

powder and solvent for solution for injection/infusion
1 vial with powder
1 vial with 5 ml water for injections
1 filter transfer device 20/20
One inner box containing:
1 disposable 10 ml syringe
1 venipuncture set
2 alcohol swabs
1 non-sterile plaster

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use

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 below 25 °C. Do not freeze.
Keep the vials in the outer carton 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

CSL Behring GmbH, 35041 Marburg, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/857/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Voncento 500 IU / 1200 IU

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
Powder vial 500 IU/1200 IU

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

Voncento 500 IU FVIII / 1200 IU VWF powder for solution for injection/infusion
For IV use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

coagulation factor VIII 500 IU
von Willebrand factor 1200 IU

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
Solvent vial label 5 ml

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

Water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
Carton 1000 IU/2400 IU

1. NAME OF THE MEDICINAL PRODUCT

Voncento 1000 IU FVIII / 2400 IU VWF (10 ml solvent) powder and solvent for solution for injection/infusionhuman coagulation factor VIII/human von Willebrand factor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

human coagulation factor VIII 1000 IU
human von Willebrand factor 2400 IU

3. LIST OF EXCIPIENTS

Other ingredients: calcium chloride, human albumin, sodium chloride, sodium citrate, sucrose, trometamol. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

powder and solvent for solution for injection/infusion
1 vial with powder
1 vial with 10 ml water for injections
1 filter transfer device 20/20
One inner box containing:
1 disposable 10 ml syringe
1 venipuncture set
2 alcohol swabs
1 non-sterile plaster

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use

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 below 25 °C. Do not freeze.
Keep the vials in the outer carton 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

CSL Behring GmbH, 35041 Marburg, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/857/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Voncento 1000 IU / 2400 IU

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
Powder vial 1000 IU/2400 IU

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

Voncento 1000 IU FVIII / 2400 IU VWF powder for solution for injection/infusion
ForIV use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

coagulation factor VIII 1000 IU
von Willebrand factor 2400 IU

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
Solvent vial label 10 ml

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

Water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
Carton administration set (inner box)

1. NAME OF THE MEDICINAL PRODUCT

Administration set

2. STATEMENT OF ACTIVE SUBSTANCE(S)

-not applicable-

3. LIST OF EXCIPIENTS

-not applicable-

4. PHARMACEUTICAL FORM AND CONTENTS

-not applicable-

5. METHOD AND ROUTE(S) OF ADMINISTRATION

-not applicable-

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

-not applicable-

7. OTHER SPECIAL WARNING(S), IF NECESSARY

-not applicable-

8. EXPIRY DATE

Exp. date

9. SPECIAL STORAGE CONDITIONS

-not applicable-

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

-not applicable-

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

-not applicable-

12. MARKETING AUTHORISATION NUMBER(S)

-not applicable-

13. BATCH NUMBER

Lot No.

14. GENERAL CLASSIFICATION FOR SUPPLY

-not applicable-

15. INSTRUCTIONS ON USE

-not applicable-

16. INFORMATION IN BRAILLE

-not applicable-

B. PACKAGE LEAFLET

Package Leaflet: Information for the user

Voncento 250 IU FVIII / 600 IU VWF (5 ml solvent) powder and solvent for solution for injection/infusion
Voncento 500 IU FVIII / 1200 IU VWF(10 ml solvent) powder and solvent for solution for injection/infusion
Voncento 500 IU FVIII / 1200 IU VWF (5 ml solvent) powder and solvent for solution for injection/infusion
Voncento 1000 IU FVIII / 2400 IU VWF (10 ml solvent) powder and solvent for solution for injection/infusion
human coagulation factor VIII,
human von Willebrand factor

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 further questions, ask your doctor, your nurse or your pharmacist.
- This medicine has been prescribed for you. 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, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Voncento is and what it is used for

The product is made from human plasma (the liquid part of the blood) and contains the active substances called human coagulation factor VIII (FVIII) and human von Willebrand factor (VWF).

Voncento is used for all age groups to prevent or to halt bleeding caused by the lack of VWF in von Willebrand disease (VWD) and the lack of FVIII in haemophilia A. Voncento is only used when treatment with another medicine, desmopressin, is not effective alone or cannot be given.

VWF and FVIII are involved in blood clotting. Lack of either factor means that blood does not clot as quickly as it should so there is an increased tendency to bleed. The replacement of VWF and FVIII by Voncento will temporarily repair the blood clotting mechanisms.

As Voncento contains both FVIII and VWF, it is important to know which factor you most need. If you have haemophilia A your doctor will prescribe you Voncento with the number of units of FVIII specified. If you have VWD your doctor will prescribe you Voncento with the number of units of VWF specified.

2. What you need to know before you use Voncento

Do not use Voncento

- If you are allergic to VWF or FVIII or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Traceability
It is strongly recommended that every time Voncento is given, you record the date of administration, the batch number and the injected volume in your treatment diary.

Talk to your doctor, nurse or pharmacist before taking Voncento.

- Allergic (hypersensitivity) reactions are possible. **If symptoms of hypersensitivity occur, you should stop using the medicine immediately and contact your doctor.** Your doctor should inform you of the **early signs of hypersensitivity reactions**. These include hives, generalised skin rash, tightness of the chest, wheezing, fall in blood pressure and anaphylaxis (a serious allergic reaction that causes severe difficulty in breathing, or dizziness).
- The formation of **inhibitors** (antibodies) is a known complication that can occur during treatment with all factor VIII medicines. These inhibitors, especially at high levels, stop the treatment working properly and you or your child will be monitored carefully for the development of these inhibitors. If your or your child's bleeding is not being controlled with Voncento, tell your doctor immediately.
- If you have been told you have heart disease or are at risk for heart disease, tell your doctor or pharmacist.
- If for the administration of Voncento you will require a central venous access device (CVAD), the risk of CVAD-related complications including local infections, bacteria in the blood (bacteremia) and the formation of a blood clot in the blood vessel (thrombosis) where the catheter is inserted should be considered by your doctor.

- von Willebrand disease
  If you have a known risk of developing blood clots, you must be monitored for early signs of thrombosis (blood clotting). Your doctor should give you treatment to prevent thrombosis.

Virus safety

When medicines are made from human blood or plasma, certain measures are put in place by the manufacturer to prevent infections being passed on to patients. These include:
- careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded,
- the testing of each donation and pools of plasma for signs of virus/infections,
- inclusion of steps in the processing of the blood or plasma that can inactivate or remove viruses.

Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.

The measures taken are considered effective for so-called "enveloped" viruses such as human immunodeficiency virus (HIV, the AIDS virus), hepatitis B virus and hepatitis C virus (which cause inflammation of the liver), and for the "non-enveloped" hepatitis A virus (which also causes inflammation of the liver).

The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19.

Parvovirus B19 infection may be serious
- for pregnant women (as there is a risk of infection of the unborn child) and

- for individuals with a weakened immune system or with an increased production of red blood cells due to certain types of anaemia (e.g. sickle cell anaemia or haemolytic anaemia).

Your doctor may recommend that you consider being vaccinated against hepatitis A and B if you regularly/repeatedly receive human plasma-derived medicines such as Voncento.

Children and adolescents

The listed warnings and precautions apply to children and adolescents.

Other medicines and Voncento

- Tell your doctor or pharmacist if you are taking, have recently taken or might take 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 or pharmacist for advice before taking this medicine.
- During pregnancy and breast-feeding, Voncento should be given only if it is clearly needed.

Driving and using machines

Voncento does not affect your ability to drive and use machines.

Voncento contains sodium

The presentations 250 IU FVIII /600 IU VWF (5 ml solvent) and 500 IU FVIII /1200 IU VWF (5 ml solvent) contain up to 14.75 mg sodium per vial (main component of cooking/table salt). This is equivalent to 0.74 % of the recommended maximum daily dietary intake of sodium for an adult.

The presentations 500 IU FVIII /1200 IU VWF (10 ml solvent) and 1000 IU FVIII /2400 IU VWF (10 ml solvent) contain up to 29.50 mg sodium per vial (main component of cooking/table salt). This is equivalent to 1.48% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use Voncento

Your treatment should be monitored by a doctor who is experienced in the treatment of blood clotting disorders.

If your doctor thinks you could administer Voncento yourself, appropriate instructions will be provided to you by your doctor. Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Dose

The amount of VWF and FVIII you need to take and the duration of treatment depend on:
- the severity of your disease
- the site and intensity of the bleeding
- your clinical condition
- your body weight

(see also section *"The following information is intended for healthcare professionals only"*).
If you have been prescribed Voncento to use at home, your doctor will make sure that you are shown how to inject it and how much to use.

Follow the directions given to you by your doctor.

Use in children and adolescents
Dosing in children and adolescents aged < 18 years is based on body weight and is therefore generally based on the same instructions as for adults. In some cases, especially in younger patients, higher doses may be needed.

If you use more Voncento than you should
Five cases of overdose have been reported from clinical trials. No side effects have been associated with these reports. The risk of developing blood clots (thrombosis) cannot be excluded in case of an extremely high dose, especially in patients with VWD.

If you forget to use Voncento
- Proceed with your next dose immediately and continue at regular intervals as advised by your doctor.
- Do not take a double dose to make up for a forgotten dose.

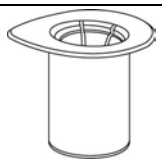
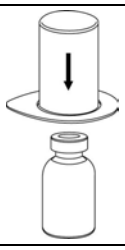
If you stop using Voncento
Do not stop using Voncento without consulting your doctor.

Reconstitution and application

General Instructions
- The powder must be mixed with the solvent (liquid) and withdrawn from the vial under aseptic conditions.
- Voncento must not be mixed with other medicines, diluents or solvents except those mentioned in section 6.
- The solution should be clear or slightly opalescent, i.e. it might be sparkling when held up to the light but must not contain any obvious particles. After filtering or withdrawal (see below) the solution should be checked by eye, before it is used. Do not use the solution if it is visibly cloudy or if it contains flakes or particles.
- Any unused product or waste material should be disposed of in accordance with local requirements and as instructed by your doctor.

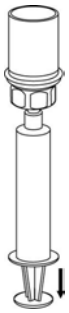
Reconstitution
Without opening the vials, warm the Voncento powder and the liquid to room or body temperature. This can be done either by leaving the vials at room temperature for about an hour, or by holding them in your hands for a few minutes.
DO NOT expose the vials to direct heat. The vials must not be heated above body temperature (37 ºC).

Carefully remove the protective caps from the vials, and clean the exposed rubber stoppers with an alcohol swab. Allow the vials to dry before opening the Mix2Vial package (which contains the filter transfer device), then follow the instructions given below.

 1	1. Open the Mix2Vial package by peeling off the lid. Do **not** remove the Mix2Vial from the blister package!
 2	2. Place the **solvent vial** on an even, clean surface and hold the vial tight. Take the Mix2Vial together with the blister package and push the spike of the **blue** adapter end **straight down** through the solvent vial stopper.

 3	3. Carefully remove the blister package from the Mix2Vial set by holding at the rim, and pulling **vertically** upwards. Make sure that you only pull away the blister package and not the Mix2Vial set.
 4	4. Place the **product vial** on an even and firm surface. Invert the solvent vial with the Mix2Vial set attached and push the spike of the **transparent** adapter end **straight down** through the product vial stopper. The solvent will automatically flow into the product vial.
 5	5. With one hand grasp the product-side of the Mix2Vial set and with the other hand grasp the solvent-side and unscrew the set carefully counterclockwise into two pieces to avoid excessive build-up of foam when dissolving the product. Discard the solvent vial with the blue Mix2Vial adapter attached.
 6	6. Gently swirl the product vial with the transparent adapter attached until the substance is fully dissolved. Do not shake.
 7	7. Draw air into an empty, sterile syringe. While the product vial is upright, connect the syringe to the Mix2Vial´s Luer Lock fitting by screwing clockwise. Inject air into the product vial.

<u>Withdrawal and Application</u>

 8	8. While keeping the syringe plunger pressed, turn the system upside down and draw the solution into the syringe by pulling the plunger back slowly.

 9	9. Now that the solution has been transferred into the syringe, firmly hold on to the barrel of the syringe (keeping the syringe plunger facing down) and disconnect the transparent Mix2Vial adapter from the syringe by unscrewing counterclockwise.

Use the venipuncture kit supplied with the product, insert the needle into a vein. Let blood flow back to the end of the tube. Attach the syringe to the threaded, locking end of the venipuncture kit. The use of plastic disposable syringes is recommended as the ground glass surfaces of all-glass syringes tend to stick with solutions of this type. **Inject/infuse the reconstituted solution slowly (at a rate not more than 6 ml per minute) into the vein** following the instructions given to you by your doctor. Take care not to get any blood in the syringe containing the product.

In case large volumes of Voncento are required, it is possible to pool several vials of Voncento together, via a commercially available infusion set (e.g. a syringe pump for giving medicines into a vein). However, in these cases the initially reconstituted solution of Voncento should not be diluted any further.

Check yourself for any side effects that might happen straight away. If you have any side effects that might be related to the administration of Voncento, the injection or infusion should be stopped (see also section 2).

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

4. Possible side effects

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

Please contact your doctor immediately if:

- **you notice symptoms of allergic reactions**
  In some cases it may progress to a serious allergic reaction (anaphylaxis) that causes severe difficulty in breathing, dizziness or shock. Allergic reactions may include the following symptoms: Swollen face, tongue, mouth or throat, difficulty in breathing and swallowing, hives, wheezing, burning and stinging where the infusion was given, chills, flushing, skin rash over the whole body, headache, fall in blood pressure, restlessness, faster heart beat, tightness of the chest (including chest pain and chest discomfort), back pain, tiredness (lethargy), nausea, vomiting, tingling.
- **you notice that the medicine stops working properly (bleeding is not stopped).**
  For children not previously treated with factor VIII medicines, inhibitor antibodies (see section 2) may form very commonly (more than 1 in 10 patients); however patients who have received previous treatment with factor VIII (more than 150 days of treatment) the risk is uncommon (less than 1 in 100 patients). If this happens your or your child's medicines may stop working properly and you or your child may experience persistent bleeding.
  You may develop an inhibitor (neutralising antibody) to VWF, in which case VWF will not work properly any more.
- **you notice any symptoms of an impaired perfusion in your extremities (e.g. cold and pale extremities) or vital organs (e.g. severe chest pain)**
  There is a risk of formation of blood clots (thrombosis), particularly in patients with known risk factors (see also section 2).

The following side effect has been observed *very commonly* (may affect more than 1 in 10 people):

- Headache

The following side effects have been observed *commonly* (may affect up to 1 in 10 people):
- Increase in body temperature

The following side effects have been observed *uncommonly* (may affect up to 1 in 100 people):
- Taste alteration (dysgeusia)
- Abnormal liver function test

Side effects in children and adolescents

Side effects in children and adolescents are expected to be the same as in adults.

Reporting of side effects
If you get any side effects, talk to your doctor, nurse or pharmacist. 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 Voncento

- 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 and carton.
- Do not store above 25 °C.
- Do not freeze.
- Voncento does not contain a preservative, so the reconstituted product should be used immediately.
- If the reconstituted product is not administered immediately, storage times and conditions prior to use are the responsibility of the user.
- Keep the vial in the outer carton in order to protect from light.
- 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 Voncento contains

The active substance is:
250 IU FVIII and 600 IU VWF per vial; after reconstitution with 5 ml of water for injection approx. 50 IU/ml FVIII and 120 IU/ml VWF.

500 IU FVIII and 1200 IU VWF per vial; after reconstitution with 10 ml of water for injection approx. 50 IU/ml FVIII and 120 IU/ml VWF.

500 IU FVIII and 1200 IU VWF per vial; after reconstitution with 5 ml of water for injection approx. 100 IU/ml FVIII and 240 IU/ml VWF.

1000 IU FVIII and 2400 IU VWF per vial; after reconstitution with 10 ml of water for injection approx. 100 IU/ml FVIII and 240 IU/ml VWF.

See section *"The following information is intended for healthcare professionals only"* for further information.

The other ingredients are:
Calcium chloride, human albumin, sodium chloride, sodium citrate, sucrose, trometamol.
See section 2 “Voncento contains sodium”.
Solvent: Water for injections

What Voncento looks like and contents of the pack

Voncento is supplied as a white powder and solvent for solution for injection/infusion.
The reconstituted solution should be clear to slightly opalescent, i.e. it might sparkle when held up to the light but must not contain any obvious particles.
The immediate container of product and solvent vial consists of glass vial with a rubber stopper, plastic disc, and aluminium cap.

Presentations
One pack with 250 IU/600 IU or 500 IU/1200 IU containing:
- 1 vial with powder
- 1 vial with 5 ml water for injections
- 1 filter transfer device 20/20
- One inner box containing:
1 disposable 10 ml syringe
1 venipuncture set
2 alcohol swabs
1 non-sterile plaster

One pack with 500 IU/1200 IU or 1000 IU/2400 IU containing:
- 1 vial with powder
- 1 vial with 10 ml water for injections
- 1 filter transfer device 20/20
- One inner box containing:
1 disposable 10 ml syringe
1 venipuncture set
2 alcohol swabs
1 non-sterile plaster

Not all pack sizes may be marketed.

Marketing Authorization Holder and Manufacturer

CSL Behring GmbH
Emil-von-Behring-Straße 76
35041 Marburg
Germany

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 European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Posology

von Willebrand disease

It is important to calculate the dose using the number of IU of VWF:RCo specified.
Generally, 1 IU/kg VWF:RCo raises the circulating level of VWF:RCo by 0.02 IU/ml (2 %).

Levels of VWF:RCo of > 0.6 IU/ml (60 %) and of FVIII:C of > 0.4 IU/ml (40 %) should be achieved.

On-demand treatment
Usually 40 - 80 IU/kg of VWF (VWF:RCo) corresponding to 20 - 40 IU FVIII:C/kg of body weight (BW) are recommended to achieve haemostasis.

An initial dose of 80 IU/kg VWF:RCo may be required, especially in patients with type 3 VWD where maintenance of adequate levels may require greater doses than in other types of VWD.

Prevention of haemorrhage in case of surgery:
For prevention of excessive bleeding during or after surgery the application should start 1 - 2 hours before the surgical procedure.

An appropriate dose should be re-administered every 12 - 24 hours. The dose and duration of the treatment depend on the clinical status of the patient, the type and severity of the bleeding, and both VWF:RCo and FVIII:C levels.

When using a FVIII-containing VWF product, the treating physician should be aware that continued treatment may cause an excessive rise in FVIII:C. After 24 - 48 hours of treatment, in order to avoid an excessive rise in FVIII:C, reduced doses and/or prolongation of the dose interval or the use of a VWF product containing a low level of FVIII should be considered.

Prophylaxis treatment
For long term prophylaxis in patients with VWD, a dose of 25 - 40 IU VWF:RCo /kg body weight should be considered at a frequency of 1 to 3 times per week. In patients with gastrointestinal bleeds or menorrhagia, shorter dose intervals or higher doses may be necessary. The dose and duration of treatment will depend on the clinical status of the patient, as well as their VWF:RCo and FVIII:C plasma levels.

Paediatric VWD population
Treatment of bleeding
Usually 40 - 80 IU/kg of von Willebrand factor (VWF:RCo) corresponding to 20 - 40 IU FVIII:C/kg of body weight (BW) are recommended in paediatric patients to treat a bleed.

Prophylaxis treatment
Patients aged 12 to 18 years old: Dosing is based on the same guidelines as for adults.

Patients aged <12 years old: Based on results from a clinical trial in which paediatric patients under 12 years of age were shown to have lower exposure of VWF, a prophylactic dose range of 40 – 80 IU VWF:RCo/kg body weight 1 to 3 times a week should be considered.
The dose and duration of treatment will depend on the clinical status of the patient, as well as their VWF:RCo and FVIII:C plasma levels.

Haemophilia A

It is important to calculate the dose using the number of IU of FVIII:C specified.
The dose and duration of the substitution therapy depend on the severity of the FVIII 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 FVIII in plasma).

1 IU of FVIII activity is equivalent to that quantity of factor VIII in 1 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 IU factor VIII per kg body weight raises the plasma factor VIII activity by about 2 % of normal activity (*in vivo* recovery 2 IU/dl). The required dose is determined using the following formula:

Required units = body weight [kg] x desired factor VIII rise [% or IU/dl] x 0.5.

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, the factor VIII activity should not fall below the given plasma activity level (in % of normal or IU/dl) within 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 (% or IU/dl)**	**Frequency of doses (hours) / Duration of therapy (days)**
Haemorrhage		
Early haemarthrosis, muscle bleeding or oral bleeding	20 - 40	Repeat infusion every 12 to 24 hours for 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 12-24 hours for 3 - 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	Repeat infusion every 24 hours for 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 continue therapy for at least another 7 days to maintain a factor VIII activity of 30% - 60% (IU/dl).

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, a precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor VIII activity) is indispensable..

Prophylaxis treatment
For long term prophylaxis in patients with severe haemophilia A, the usual dose is 20 to 40 IU of FVIII per kg body weight at intervals of 2 to 3 days. In some cases, especially in younger patients, shorter dose intervals or higher doses may be necessary.

Paediatric haemophilia A population
Dosing in in haemophilia A in children and adolescents aged < 18 years is based on body weight and is therefore generally based on the same guidelines as for adults. In some cases shorter dose intervals or higher doses may be necessary. The frequency of administration should always be oriented to the clinical effectiveness in the individual case.

Elderly
No dose adjustment is necessary for the older people.