SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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 the10 ml water for injections provided, the solution contains 100 IU/ml of FVIII and 240 IU/ml of VWF.

* 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.

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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.

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.

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 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 factor VIII 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 4.8 and 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 500 IU FVIII / 1200 IU VWF (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 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 post-marketing 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
Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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

<u>von Willebrand disease</u>
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.

<u>Haemophilia A</u>
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, annualised 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 % 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 t½ of VWF markers was between 10.00 and 13.48 h whereas FVIII:C had a longer t½ 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**		**<6 years**		**6-12**		**<6 years**		**6-12**		**<6 years**		**6-12**	

			years				years				years				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 t½ 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 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

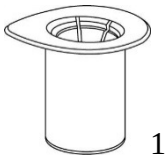
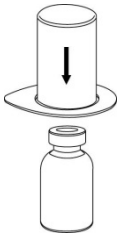
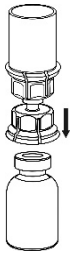
One inner box containing:
1 disposable 10 ml syringe
1 venipuncture set
2 alcohol swabs
1 non-sterile plaster

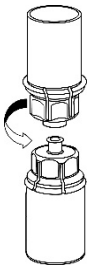
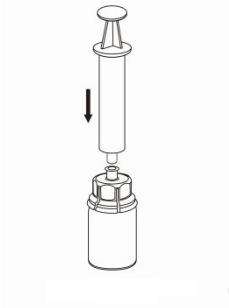
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

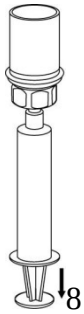
General instructions
The solution should be clear or slightly opalescent. After filtering/withdrawal (see below) the reconstituted product should be inspected visually for particulate matter and discoloration prior to administration. Do not use visibly cloudy solutions or solutions still containing flakes 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-Strasse 76
35041 Marburg
Germany

8. MARKETING AUTHORIZATION NUMBER(S)

PLGB 15036/0149

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

01 January 2021

10 DATE OF REVISION OF THE TEXT

14/05/2024