ANNEX I

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

1. **NAME OF THE MEDICINAL PRODUCT**

Voncento 250 IU / 600 IU powder and solvent for solution for injection/infusion

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

One vial contains nominally:
- 250 IU* human coagulation factor VIII** (FVIII).
- 600 IU*** human von Willebrand factor** (VWF).

After reconstitution with 5 ml the solution contains 50 IU/ml of FVIII and 120 IU/ml of VWF.

Excipient with known effect:

Sodium approximately 128.2 mmol/l (2.95 mg/ml).

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**

von Willebrand disease (VWD)

Treatment of haemorrhage or prevention and treatment of 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.

* 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:RCo 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:RCo/mg protein.
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 for an individual patient on the use of home treatment of bleedings in patients with VWD
and prophylaxis and treatment of bleedings in patients 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.

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.

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).

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 FVIII administered is expressed in International Units (IU), which is related to
the current WHO standard for FVIII products. FVIII activity in plasma is expressed either as a
percentage (relative to normal human plasma) or in IU (relative to an International Standard for FVIII
in plasma).

1 IU of FVIII activity is equivalent to that quantity of FVIII in 1 ml of normal human plasma.

On demand treatment
The calculation of the required dose of FVIII is based on the empirical finding that 1 IU FVIII per kg
body weight raises the plasma FVIII 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 FVIII 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 FVIII 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:

<table>
<thead>
<tr>
<th>Degree of haemorrhage / Type of surgical procedure</th>
<th>FVIII level required (% or IU/dl)</th>
<th>Frequency of doses (hours) / Duration of therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early haemarthrosis, muscle bleeding or oral bleeding</td>
<td>20 - 40</td>
<td>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.</td>
</tr>
<tr>
<td>More extensive haemarthrosis, muscle bleeding or haematoma</td>
<td>30 - 60</td>
<td>Repeat infusion every 12 - 24 hours for 3 - 4 days or more until pain and acute disability are resolved.</td>
</tr>
<tr>
<td>Life-threatening haemorrhages</td>
<td>60 - 100</td>
<td>Repeat infusion every 8 - 24 hours until threat is resolved.</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor including tooth extraction</td>
<td>30 - 60</td>
<td>Repeat infusion every 24 hours for at least 1 day, until healing is achieved.</td>
</tr>
<tr>
<td>Major 80 - 100 (pre- and postoperative)</td>
<td>Repeat infusion every 8 - 24 hours until adequate wound healing, then continue therapy for at least another 7 days to maintain a FVIII activity of 30 % - 60 % (IU/dl).</td>
<td></td>
</tr>
</tbody>
</table>

During the course of treatment, appropriate determination of FVIII levels is advised to guide the dose to be administered and the frequency of repeated infusions. In the case of major surgical interventions in particular, a precise monitoring of the substitution therapy by means of coagulation analysis (plasma FVIII activity) is indispensable. Individual patients may vary in their response to FVIII, achieving different levels of in vivo recovery and demonstrating different half-lives.

Prophylaxis
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.

Previously untreated patients
The safety and efficacy of Voncento in previously untreated patients have not yet been established.
Paediatric population
Dosing in VWD and haemophilia A in adolescents aged 12 to 18 years old is based on body weight and is therefore generally based on the same guidelines as for adults. The frequency of administration should always be oriented to the clinical effectiveness in the individual case.

The safety and efficacy of Voncento in children < 12 years have not been established. No data are available.

Older people
No dose adjustment is necessary for the older people.

Method of administration
For intravenous use.
Reconstitute the product as described in 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
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.
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.

**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 FVIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the FVIII procoagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma, using the modified assay. The risk of developing inhibitors is correlated to the exposure to factor VIII, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days.

Cases of recurrent inhibitor (low titre) have been observed after switching from one factor VIII product to another in previously treated patients with more than 100 exposure days who have a previous history of inhibitor development. Therefore, it is recommended to monitor all patients carefully for inhibitor occurrence following any product switch.

In general, all patients treated with human coagulation FVIII 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. The management of such patients should be directed by physicians with experience in the care of haemophilia A patients and those with factor VIII inhibitors.

**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**

This medicine contains up to 14.75 mg (0.64 mmol) sodium per vial. To be taken into consideration by patients on a controlled sodium diet.
4.5 Interaction with other medicinal products and other forms of interaction

No interaction 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 in adults and adolescents 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.

<table>
<thead>
<tr>
<th>MedDRA Standard System Organ Class</th>
<th>Adverse Reaction</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>FVIII inhibition</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>VWF inhibition</td>
<td>Very rare</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity (including tachycardia, chest pain, chest discomfort and back pain)</td>
<td>Very rare</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dysgeusia</td>
<td>Very rare</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Thromboembolic event</td>
<td>Very rare</td>
</tr>
<tr>
<td>General disorders and</td>
<td>Pyrexia</td>
<td>Very rare</td>
</tr>
<tr>
<td>administration site conditions</td>
<td>Headache</td>
<td>Very rare</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>---------</td>
<td>-----------</td>
</tr>
<tr>
<td>Investigations</td>
<td>Liver function test abnormal</td>
<td>Very rare</td>
</tr>
</tbody>
</table>

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:** Patients with haemophilia A may develop neutralising antibodies (inhibitors) to FVIII. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted. There is no experience from clinical trials with Voncento in previously untreated patients (PUPs). Therefore, no valid figures on the incidence of clinically relevant specific inhibitors are currently available.

**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

One case of overdose (twice the amount of the recommended dose) has been observed in clinical trials. No severe adverse reactions were associated with this case.

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.

The European Medicines Agency has deferred the obligation to submit the results of studies with Voncento in patients from birth to less than 12 years of age with VWD.

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.

The European Medicines Agency has deferred the obligation to submit the results of studies with Voncento in patients from birth to less than 12 years of age with haemophilia A.
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 with VWD, the following pharmacokinetic characteristics for VWF:RCo, VWF:Ag, VWF:CB and FVIII:C were observed:

<table>
<thead>
<tr>
<th>parameter</th>
<th>VWF:RCo</th>
<th>VWF:Ag</th>
<th>VWF:CB</th>
<th>FVIII:C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
<td>SD</td>
<td>range</td>
</tr>
<tr>
<td>Incremental recovery</td>
<td>12</td>
<td>0.017</td>
<td>0.002</td>
<td>0.01-0.02</td>
</tr>
<tr>
<td>(kg/mL)</td>
<td>8</td>
<td>13.7</td>
<td>9.2</td>
<td>6.1-35.1</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>12</td>
<td>17.7</td>
<td>9.7</td>
<td>12.7-22.7</td>
</tr>
<tr>
<td>AUC_{0-72} (h*IU/mL)</td>
<td>8</td>
<td>14.0</td>
<td>5.0</td>
<td>8.6-25.5</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>12</td>
<td>1.65</td>
<td>0.63</td>
<td>0.93-3.36</td>
</tr>
<tr>
<td>C_{max} (IU/mL)</td>
<td>12</td>
<td>0.25*</td>
<td>0.25-1.03</td>
<td>12</td>
</tr>
<tr>
<td>T_{max} (h)</td>
<td>12</td>
<td>0.01</td>
<td>0.01</td>
<td>0.00-0.03</td>
</tr>
<tr>
<td>C_{min} (IU/mL)</td>
<td>12</td>
<td>6.09</td>
<td>1.66</td>
<td>3.06-9.32</td>
</tr>
<tr>
<td>Total clearance (mL/(h*kg)</td>
<td>8</td>
<td>74.8</td>
<td>35.3</td>
<td>44.7-158.0</td>
</tr>
</tbody>
</table>

*median

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; SD = standard deviation; t_{max} = time the 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

The relative HMW VWF of Voncento compared to normal human plasma is on average 86%. The relative expression of HMW VWF multimers in VWD patients after infusion of Voncento was approximately 10% (using a semi-quantitative multimer analysis).
**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 with haemophilia A, the following pharmacokinetic characteristics for FVIII:C were observed:

<table>
<thead>
<tr>
<th>parameter</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incremental recovery (kg/mL)</td>
<td>16</td>
<td>0.021</td>
<td>0.006</td>
<td>0.011-0.032</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>16</td>
<td>13.40</td>
<td>2.53</td>
<td>8.78-18.51</td>
</tr>
<tr>
<td>AUC$_{0-48}$ (h*IU/mL)</td>
<td>16</td>
<td>13.79</td>
<td>3.79</td>
<td>7.04-21.79</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>16</td>
<td>16.96</td>
<td>3.68</td>
<td>11.29-26.31</td>
</tr>
<tr>
<td>C$_{\text{max}}$ (IU/mL)</td>
<td>16</td>
<td>1.07</td>
<td>0.28</td>
<td>0.57-1.57</td>
</tr>
<tr>
<td>T$_{\text{max}}$ (h)</td>
<td>16</td>
<td>0.81</td>
<td>0.94</td>
<td>0.42-4.03</td>
</tr>
<tr>
<td>C$_{\text{min}}$ (IU/mL)</td>
<td>16</td>
<td>0.060</td>
<td>0.028</td>
<td>0.021-0.111</td>
</tr>
<tr>
<td>Total clearance (mL/(h*kg))</td>
<td>16</td>
<td>3.92</td>
<td>1.22</td>
<td>2.30-7.11</td>
</tr>
<tr>
<td>V$_{\text{ss}}$ (ml/kg)</td>
<td>16</td>
<td>65.33</td>
<td>20.65</td>
<td>35.07-113.06</td>
</tr>
</tbody>
</table>

AUC = area under the curve; C$_{\text{max}}$ = maximum plasma concentration; C$_{\text{min}}$ = minimum plasma concentration; IU = International Unit; MRT = mean residence time; N = number of subjects; SD = standard deviation; T$_{\text{max}}$ = time the maximum concentration occurs; V$_{\text{ss}}$ = volume of distribution at steady state; FVIII:C = Factor VIII: Coagulant

**Paediatric population**

No pharmacokinetic data are available in patients younger than 12 years.

### 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.

After reconstitution the 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 and would normally not be longer than 24 hours at 2 to 8 °C.

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

Immediate containers

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).

Presentation

Pack with 250 IU/600 IU:
1 powder vial
1 solvent vial

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 aseptic solution and allowed to dry prior to opening the Mix2Vial package.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1. Open the Mix2Vial package by peeling off the lid. Do not remove the Mix2Vial from the blister package!</td>
</tr>
<tr>
<td>2</td>
<td>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.</td>
</tr>
<tr>
<td>3</td>
<td>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.</td>
</tr>
<tr>
<td>4</td>
<td>4. Place the powder 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.</td>
</tr>
<tr>
<td>5</td>
<td>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 into two pieces to avoid excessive build-up of foam when dissolving the product. Discard the solvent vial with the blue Mix2Vial adapter attached.</td>
</tr>
<tr>
<td>6</td>
<td>6. Gently swirl the product vial with the transparent adapter attached until the substance is fully dissolved. Do not shake.</td>
</tr>
</tbody>
</table>
7. Draw air into an empty, sterile syringe. While the product vial is upright, connect the syringe to the Mix2Vial’s Luer Lock fitting. Inject air into the product vial.

Withdrawal and application

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. 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.

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 drugs). However, in these cases the initially reconstituted solution of Voncento should not be diluted any further.

Administer 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

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorisation: 12 August 2013

10. DATE OF REVISION OF THE TEXT

November 2014

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu
This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Voncento 500 IU /1200 IU powder and solvent for solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains nominally:
- 500 IU* human coagulation factor VIII** (FVIII).
- 1200 IU*** human von Willebrand factor** (VWF)
After reconstitution with 10 ml the solution contains 50 IU/ml of FVIII and 120 IU/ml of VWF.

Excipient with known effect:

Sodium approximately 128.2 mmol/l (2.95 mg/ml).
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

von Willebrand disease (VWD)

Treatment of haemorrhage or prevention and treatment of 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.

* 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:RCo 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:RCo/mg protein.
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 for an individual patient on the use of home treatment of bleedings in patients with VWD and prophylaxis and treatment of bleedings in patients 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.

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.

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).

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 FVIII administered is expressed in International Units (IU), which is related to the current WHO standard for FVIII products. FVIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or in IU (relative to an International Standard for FVIII in plasma).

1 IU of FVIII activity is equivalent to that quantity of FVIII in 1 ml of normal human plasma.

On demand treatment
The calculation of the required dose of FVIII is based on the empirical finding that 1 IU FVIII per kg body weight raises the plasma FVIII 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 FVIII 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 FVIII 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:

<table>
<thead>
<tr>
<th>Degree of haemorrhage / Type of surgical procedure</th>
<th>FVIII level required (% or IU/dl)</th>
<th>Frequency of doses (hours) / Duration of therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early haemarthrosis, muscle bleeding or oral bleeding</td>
<td>20 - 40</td>
<td>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.</td>
</tr>
<tr>
<td>More extensive haemarthrosis, muscle bleeding or haematoma</td>
<td>30 - 60</td>
<td>Repeat infusion every 12 - 24 hours for 3 - 4 days or more until pain and acute disability are resolved.</td>
</tr>
<tr>
<td>Life-threatening haemorrhages</td>
<td>60 - 100</td>
<td>Repeat infusion every 8 - 24 hours until threat is resolved.</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor including tooth extraction</td>
<td>30 - 60</td>
<td>Repeat infusion every 24 hours for at least 1 day, until healing is achieved.</td>
</tr>
<tr>
<td>Major 80 - 100 (pre- and postoperative)</td>
<td></td>
<td>Repeat infusion every 8 - 24 hours until adequate wound healing, then continue therapy for at least another 7 days to maintain a FVIII activity of 30 % - 60 % (IU/dl).</td>
</tr>
</tbody>
</table>

During the course of treatment, appropriate determination of FVIII levels is advised to guide the dose to be administered and the frequency of repeated infusions. In the case of major surgical interventions in particular, a precise monitoring of the substitution therapy by means of coagulation analysis (plasma FVIII activity) is indispensable. Individual patients may vary in their response to FVIII, achieving different levels of in vivo recovery and demonstrating different half-lives.

Prophylaxis
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.

Previously untreated patients
The safety and efficacy of Voncento in previously untreated patients have not yet been established.
**Paediatric population**
Dosing in VWD and haemophilia A in adolescents aged 12 to 18 years old is based on body weight and is therefore generally based on the same guidelines as for adults. The frequency of administration should always be oriented to the clinical effectiveness in the individual case.

The safety and efficacy of Voncento in children < 12 years have not been established. No data are available.

**Older people**
No dose adjustment is necessary for the older people.

**Method of administration**
For intravenous use.
Reconstitute the product as described in 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**

**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.
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.

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 FVIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the FVIII procoagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma, using the modified assay. The risk of developing inhibitors is correlated to the exposure to factor VIII, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days.

Cases of recurrent inhibitor (low titre) have been observed after switching from one factor VIII product to another in previously treated patients with more than 100 exposure days who have a previous history of inhibitor development. Therefore, it is recommended to monitor all patients carefully for inhibitor occurrence following any product switch.

In general, all patients treated with human coagulation FVIII 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. The management of such patients should be directed by physicians with experience in the care of haemophilia A patients and those with factor VIII inhibitors.

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

This medicine contains up to 29.50 mg (1.28 mmol) sodium per vial. To be taken into consideration by patients on a controlled sodium diet.
4.5 Interaction with other medicinal products and other forms of interaction

No interaction 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 in adults and adolescents 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).

<table>
<thead>
<tr>
<th>MedDRA Standard System Organ Class</th>
<th>Adverse Reaction</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>FVIII inhibition</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>VWF inhibition</td>
<td>Very rare</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity (including tachycardia, chest pain, chest discomfort and back pain)</td>
<td>Very rare</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dysgeusia</td>
<td>Very rare</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Thromboembolic event</td>
<td>Very rare</td>
</tr>
<tr>
<td>General disorders and</td>
<td>Pyrexia</td>
<td>Very rare</td>
</tr>
</tbody>
</table>
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_: Patients with haemophilia A may develop neutralising antibodies (inhibitors) to FVIII. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted. There is no experience from clinical trials with Voncento in previously untreated patients (PUPs). Therefore, no valid figures on the incidence of clinically relevant specific inhibitors are currently available.

_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**

One case of overdose (twice the amount of the recommended dose) has been observed in clinical trials. No severe adverse reactions were associated with this case.

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.

The European Medicines Agency has deferred the obligation to submit the results of studies with Voncento in patients from birth to less than 12 years of age with VWD.

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.

The European Medicines Agency has deferred the obligation to submit the results of studies with Voncento in patients from birth to less than 12 years of age with haemophilia A.
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 with VWD, the following pharmacokinetic characteristics for VWF:RCo, VWF:Ag, VWF:CB and FVIII:C were observed:

<table>
<thead>
<tr>
<th>parameter</th>
<th>VWF:RCo</th>
<th>VWF:Ag</th>
<th>VWF:CB</th>
<th>FVIII:C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incremental recovery (kg/mL)</td>
<td>N</td>
<td>Mean</td>
<td>SD</td>
<td>range</td>
</tr>
<tr>
<td>12</td>
<td>0.017</td>
<td>0.002</td>
<td>0.01-0.02</td>
<td></td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>N</td>
<td>Mean</td>
<td>SD</td>
<td>range</td>
</tr>
<tr>
<td>8</td>
<td>13.7</td>
<td>9.2</td>
<td>6.1-35.1</td>
<td>22.7</td>
</tr>
<tr>
<td>AUC_0-72 (h*IU/mL)</td>
<td>N</td>
<td>Mean</td>
<td>SD</td>
<td>range</td>
</tr>
<tr>
<td>8</td>
<td>17.7</td>
<td>9.7</td>
<td>12.7-22.7</td>
<td>64.7</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (IU/mL)</td>
<td>N</td>
<td>Mean</td>
<td>SD</td>
<td>range</td>
</tr>
<tr>
<td>8</td>
<td>1.65</td>
<td>0.63</td>
<td>0.93-3.36</td>
<td>3.66</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>N</td>
<td>Mean</td>
<td>SD</td>
<td>range</td>
</tr>
<tr>
<td>8</td>
<td>0.25&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.25-1.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;min&lt;/sub&gt; (IU/mL)</td>
<td>N</td>
<td>Mean</td>
<td>SD</td>
<td>range</td>
</tr>
<tr>
<td>8</td>
<td>0.01</td>
<td>0.01</td>
<td>0.00-0.03</td>
<td>0.17</td>
</tr>
<tr>
<td>Total clearance (mL/(h*kg))</td>
<td>N</td>
<td>Mean</td>
<td>SD</td>
<td>range</td>
</tr>
<tr>
<td>8</td>
<td>6.09</td>
<td>1.66</td>
<td>3.06-9.32</td>
<td>4.78</td>
</tr>
<tr>
<td>V&lt;sub&gt;ss&lt;/sub&gt; (ml/kg)</td>
<td>N</td>
<td>Mean</td>
<td>SD</td>
<td>range</td>
</tr>
<tr>
<td>8</td>
<td>74.8</td>
<td>35.3</td>
<td>44.7-158.0</td>
<td>128.4</td>
</tr>
</tbody>
</table>

<sup>a</sup>median

AUC = area under the curve; C<sub>max</sub> = maximum plasma concentration; C<sub>min</sub> = minimum plasma concentration; IU = International Unit; MRT = mean residence time; N = number of subjects; SD = standard deviation; t<sub>max</sub> = time the maximum concentration occurs; V<sub>ss</sub> = 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 HMW VWF of Voncento compared to normal human plasma is on average 86%. The relative expression of HMW VWF multimers in VWD patients after infusion of Voncento was approximately 10% (using a semi-quantitative multimer analysis).
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 with haemophilia A, the following pharmacokinetic characteristics for FVIII:C were observed:

<table>
<thead>
<tr>
<th>parameter</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incremental recovery (kg/mL)</td>
<td>16</td>
<td>0.021</td>
<td>0.006</td>
<td>0.011-0.032</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>16</td>
<td>13.40</td>
<td>2.53</td>
<td>8.78-18.51</td>
</tr>
<tr>
<td>AUC$_{0-48}$ (h*IU/mL)</td>
<td>16</td>
<td>13.79</td>
<td>3.79</td>
<td>7.04-21.79</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>16</td>
<td>16.96</td>
<td>3.68</td>
<td>11.29-26.31</td>
</tr>
<tr>
<td>C$_{max}$ (IU/mL)</td>
<td>16</td>
<td>1.07</td>
<td>0.28</td>
<td>0.57-1.57</td>
</tr>
<tr>
<td>T$_{max}$ (h)</td>
<td>16</td>
<td>0.81</td>
<td>0.94</td>
<td>0.42-4.03</td>
</tr>
<tr>
<td>C$_{min}$ (IU/mL)</td>
<td>16</td>
<td>0.060</td>
<td>0.028</td>
<td>0.021-0.111</td>
</tr>
<tr>
<td>Total clearance (mL/(h*kg))</td>
<td>16</td>
<td>3.92</td>
<td>1.22</td>
<td>2.30-7.11</td>
</tr>
<tr>
<td>V$_{ss}$ (ml/kg)</td>
<td>16</td>
<td>65.33</td>
<td>20.65</td>
<td>35.07-113.06</td>
</tr>
</tbody>
</table>

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; SD = standard deviation; T$_{max}$ = time the maximum concentration occurs; V$_{ss}$ = volume of distribution at steady state; FVIII:C = Factor VIII: Coagulant

Paediatric population

No pharmacokinetic data are available in patients younger than 12 years.

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.

After reconstitution the 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 and would normally not be longer than 24 hours at 2 to 8 °C.

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

Immediate containers

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).

Presentation

Pack with 500/1200 IU:
1 powder vial
1 solvent vial

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 aseptic solution and allowed to dry prior to opening the Mix2Vial package.

1. Open the Mix2Vial package by peeling off the lid. Do not remove the Mix2Vial from the blister package!

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. 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. Place the powder 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. 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 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. Gently swirl the product vial with the transparent adapter attached until the substance is fully dissolved. Do not shake.
7. Draw air into an empty, sterile syringe. While the product vial is upright, connect the syringe to the Mix2Vial’s Luer Lock fitting. Inject air into the product vial.

Withdrawal and application

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. 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.

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 drugs). However, in these cases the initially reconstituted solution of Voncento should not be diluted any further.

Administer 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/1/13/857/002

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorisation: 12 August 2013

10. DATE OF REVISION OF THE TEXT

November 2014

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu
This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Voncento 500 IU / 1200 IU powder and solvent for solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains nominally:
- 500 IU* human coagulation factor VIII** (FVIII)
- 1200 IU*** human von Willebrand factor** (VWF).
After reconstitution with 5 ml the solution contains 100 IU/ml of FVIII and 240 IU/ml of VWF.

Excipient with known effect:
Sodium approximately 128.2 mmol/l (2.95 mg/ml).
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

von Willebrand disease (VWD)

Treatment of haemorrhage or prevention and treatment of 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.

* 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:RCo 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:RCo/mg protein.
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 for an individual patient on the use of home treatment of bleedings in patients with VWD and prophylaxis and treatment of bleedings in patients 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.

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. 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).

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 FVIII administered is expressed in International Units (IU), which is related to the current WHO standard for FVIII products. FVIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or in IU (relative to an International Standard for FVIII in plasma).

1 IU of FVIII activity is equivalent to that quantity of FVIII in 1 ml of normal human plasma.
On demand treatment

The calculation of the required dose of FVIII is based on the empirical finding that 1 IU FVIII per kg body weight raises the plasma FVIII 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 FVIII 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 FVIII 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:

<table>
<thead>
<tr>
<th>Degree of haemorrhage / Type of surgical procedure</th>
<th>FVIII level required (% or IU/dl)</th>
<th>Frequency of doses (hours) / Duration of therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early haemarthrosis, muscle bleeding or oral bleeding</td>
<td>20 - 40</td>
<td>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.</td>
</tr>
<tr>
<td>More extensive haemarthrosis, muscle bleeding or haematoma</td>
<td>30 - 60</td>
<td>Repeat infusion every 12 - 24 hours for 3 - 4 days or more until pain and acute disability are resolved.</td>
</tr>
<tr>
<td>Life-threatening haemorrhages</td>
<td>60 - 100</td>
<td>Repeat infusion every 8 - 24 hours until threat is resolved.</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor including tooth extraction</td>
<td>30 - 60</td>
<td>Repeat infusion every 24 hours for at least 1 day, until healing is achieved.</td>
</tr>
<tr>
<td>Major 80 - 100 (pre- and postoperative)</td>
<td></td>
<td>Repeat infusion every 8 - 24 hours until adequate wound healing, then continue therapy for at least another 7 days to maintain a FVIII activity of 30% - 60% (IU/dl).</td>
</tr>
</tbody>
</table>

During the course of treatment, appropriate determination of FVIII levels is advised to guide the dose to be administered and the frequency of repeated infusions. In the case of major surgical interventions in particular, a precise monitoring of the substitution therapy by means of coagulation analysis (plasma FVIII activity) is indispensable. Individual patients may vary in their response to FVIII, achieving different levels of in vivo recovery and demonstrating different half-lives.

Prophylaxis

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

Paediatric population
Dosing in VWD and haemophilia A in adolescents aged 12 to 18 years old is based on body weight and is therefore generally based on the same guidelines as for adults. The frequency of administration should always be oriented to the clinical effectiveness in the individual case.

The safety and efficacy of Voncento in children < 12 years have not been established. No data are available.

Older people
No dose adjustment is necessary for the older people.

Method of administration

For intravenous use.
Reconstitute the product as described in 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

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.

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.

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 FVIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the FVIII procoagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma, using the modified assay. The risk of developing inhibitors is correlated to the exposure to factor VIII, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days.

Cases of recurrent inhibitor (low titre) have been observed after switching from one factor VIII product to another in previously treated patients with more than 100 exposure days who have a previous history of inhibitor development. Therefore, it is recommended to monitor all patients carefully for inhibitor occurrence following any product switch.

In general, all patients treated with human coagulation FVIII 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. The management of such patients should be directed by physicians with experience in the care of haemophilia A patients and those with factor VIII inhibitors.

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

This medicine contains up to 14.75 mg (0.64 mmol) sodium per vial. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction 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 in adults and adolescents 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).
<table>
<thead>
<tr>
<th>MedDRA Standard System Organ Class</th>
<th>Adverse Reaction</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>FVIII inhibition</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>VWF inhibition</td>
<td>Very rare</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity (including tachycardia, chest pain, chest discomfort and back pain)</td>
<td>Very rare</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dysgeusia</td>
<td>Very rare</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Thromboembolic event</td>
<td>Very rare</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Pyrexia</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>Very rare</td>
</tr>
<tr>
<td>Investigations</td>
<td>Liver function test abnormal</td>
<td>Very rare</td>
</tr>
</tbody>
</table>

**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:* Patients with haemophilia A may develop neutralising antibodies (inhibitors) to FVIII. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted. There is no experience from clinical trials with Voncento in previously untreated patients (PUPs). Therefore, no valid figures on the incidence of clinically relevant specific inhibitors are currently available.

*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

One case of overdose (twice the amount of the recommended dose) has been observed in clinical trials. No severe adverse reactions were associated with this case.

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.

The European Medicines Agency has deferred the obligation to submit the results of studies with Voncento in patients from birth to less than 12 years of age with VWD.

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.

The European Medicines Agency has deferred the obligation to submit the results of studies with Voncento in patients from birth to less than 12 years of age with haemophilia A.

### 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 with VWD, the following pharmacokinetic characteristics for VWF:RCO, VWF:Ag, VWF:CB and FVIII:C were observed:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>VWF:RCO</th>
<th>VWF:Ag</th>
<th>VWF:CB</th>
<th>FVIII:C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incremental recovery (kg/mL)</strong></td>
<td>12 0.017 0.002 0.01-0.02</td>
<td>12 0.018 0.002 0.01-0.02</td>
<td>12 0.020 0.004 0.02-0.02</td>
<td>12 0.025 0.006 0.02-0.04</td>
</tr>
<tr>
<td><strong>Half-life (h)</strong></td>
<td>8 13.7 9.2 6.1-35.1</td>
<td>12 18.3 4.0 11.4-27.0</td>
<td>12 16.0 4.6 9.4-25.1</td>
<td>10 28.0 15.7 7.7-57.5</td>
</tr>
<tr>
<td><strong>AUC&lt;sub&gt;0-72&lt;/sub&gt; (h*IU/mL)</strong></td>
<td>12 17.7 9.7 12.7-22.7</td>
<td>12 37.8 13.3 22.6-64.7</td>
<td>12 24.8 8.8 14.8-41.1</td>
<td>11 34.0 16.2 13.2-66.8</td>
</tr>
<tr>
<td><strong>MRT (h)</strong></td>
<td>8 14.0 5.0 8.6-25.5</td>
<td>12 23.6 5.0 15.3-33.6</td>
<td>12 20.0 4.4 11.6-28.6</td>
<td>10 43.1 22.1 15.6-85.1</td>
</tr>
<tr>
<td><strong>C&lt;sub&gt;max&lt;/sub&gt; (IU/mL)</strong></td>
<td>12 1.65 0.63 0.93-3.36</td>
<td>12 2.29 0.59 1.52-3.66</td>
<td>12 1.68 0.50 1.04-2.66</td>
<td>12 0.96 0.25 0.57-1.32</td>
</tr>
<tr>
<td><strong>T&lt;sub&gt;max&lt;/sub&gt; (h)</strong></td>
<td>12 0.25&lt;sup&gt;a&lt;/sup&gt; 0.25-1.03</td>
<td>12 0.25&lt;sup&gt;a&lt;/sup&gt; 0.25-1.00</td>
<td>12 0.25&lt;sup&gt;a&lt;/sup&gt; 0.25-1.00</td>
<td>12 1.00&lt;sup&gt;a&lt;/sup&gt; 0.25-30.00</td>
</tr>
<tr>
<td><strong>C&lt;sub&gt;min&lt;/sub&gt; (IU/mL)</strong></td>
<td>12 0.01 0.01 0.00-0.03</td>
<td>12 0.10 0.05 0.02-0.17</td>
<td>12 0.05 0.02 0.02-0.09</td>
<td>12 0.21 0.18 0.03-0.59</td>
</tr>
<tr>
<td><strong>Total clearance (mL/(h*kg))</strong></td>
<td>12 6.09 1.66 3.06-9.32</td>
<td>12 3.57 0.69 2.61-4.78</td>
<td>12 3.53 0.89 2.32-4.77</td>
<td>11 1.33 0.59 0.62-2.47</td>
</tr>
<tr>
<td><strong>V&lt;sub&gt;s&lt;/sub&gt; (ml/kg)</strong></td>
<td>8 74.8 35.3 44.7-158.0</td>
<td>12 82.8 18.6 64.5-128.4</td>
<td>12 68.6 15.7 47.5-93.7</td>
<td>10 48.1 15.3 24.8-72.9</td>
</tr>
</tbody>
</table>

<sup>a</sup>median

AUC = area under the curve; C<sub>max</sub> = maximum plasma concentration; C<sub>min</sub> = minimum plasma concentration; IU = International Unit; MRT = mean residence time; N = number of subjects; SD = standard deviation; t<sub>max</sub> = time the maximum concentration occurs; V<sub>s</sub> = 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 HMW VWF of Voncento compared to normal human plasma is on average 86%. The relative expression of HMW VWF multimers in VWD patients after infusion of Voncento was approximately 10% (using a semi-quantitative multimer analysis).
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 with haemophilia A, the following pharmacokinetic characteristics for FVIII:C were observed:

<table>
<thead>
<tr>
<th>parameter</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incremental recovery (kg/mL)</td>
<td>16</td>
<td>0.021</td>
<td>0.006</td>
<td>0.011-0.032</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>16</td>
<td>13.40</td>
<td>2.53</td>
<td>8.78-18.51</td>
</tr>
<tr>
<td>AUC$_{0-48}$ (h*IU/mL)</td>
<td>16</td>
<td>13.79</td>
<td>3.79</td>
<td>7.04-21.79</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>16</td>
<td>16.96</td>
<td>3.68</td>
<td>11.29-26.31</td>
</tr>
<tr>
<td>C$_{max}$ (IU/mL)</td>
<td>16</td>
<td>1.07</td>
<td>0.28</td>
<td>0.57-1.57</td>
</tr>
<tr>
<td>T$_{max}$ (h)</td>
<td>16</td>
<td>0.81</td>
<td>0.94</td>
<td>0.42-4.03</td>
</tr>
<tr>
<td>C$_{min}$ (IU/mL)</td>
<td>16</td>
<td>0.060</td>
<td>0.028</td>
<td>0.021-0.111</td>
</tr>
<tr>
<td>Total clearance (mL/h*kg)</td>
<td>16</td>
<td>3.92</td>
<td>1.22</td>
<td>2.30-7.11</td>
</tr>
<tr>
<td>V$_{ss}$ (ml/kg)</td>
<td>16</td>
<td>65.33</td>
<td>20.65</td>
<td>35.07-113.06</td>
</tr>
</tbody>
</table>

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; SD = standard deviation; $t_{max}$ = time the maximum concentration occurs; $V_{ss}$ = volume of distribution at steady state; FVIII:C = Factor VIII:Coagulant

Paediatric population

No pharmacokinetic data are available in patients younger than 12 years.

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.

After reconstitution the 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 and would normally not be longer than 24 hours at 2 to 8 °C.

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

Immediate containers

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).

Presentation

Pack with 500 IU/1200 IU:
1 powder vial
1 solvent vial

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 aseptic solution and allowed to dry prior to opening the Mix2Vial package.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Open the Mix2Vial package by peeling off the lid. Do not remove the Mix2Vial from the blister package!</td>
</tr>
<tr>
<td>2.</td>
<td>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.</td>
</tr>
<tr>
<td>3.</td>
<td>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.</td>
</tr>
<tr>
<td>4.</td>
<td>Place the powder 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.</td>
</tr>
<tr>
<td>5.</td>
<td>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 into two pieces to avoid excessive build-up of foam when dissolving the product. Discard the solvent vial with the blue Mix2Vial adapter attached.</td>
</tr>
<tr>
<td>6.</td>
<td>Gently swirl the product vial with the transparent adapter attached until the substance is fully dissolved. Do not shake.</td>
</tr>
</tbody>
</table>
Withdrawal and application

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. 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.

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 drugs). However, in these cases the initially reconstituted solution of Voncento should not be diluted any further.

Administer 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/1/13/857/003

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorisation: 12 August 2013

10. DATE OF REVISION OF THE TEXT

November 2014

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu
1. NAME OF THE MEDICINAL PRODUCT

Voncento 1000 IU / 2400 IU powder and solvent for solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains nominally:
- 1000 IU* human coagulation factor VIII** (FVIII)
- 2400 IU*** human von Willebrand factor** (VWF)

After reconstitution with 10 ml the solution contains 100 IU/ml of FVIII and 240 IU/ml of VWF.

Excipient with known effect:

Sodium approximately 128.2 mmol/l (2.95 mg/ml).
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

von Willebrand disease (VWD)

Treatment of haemorrhage or prevention and treatment of 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.

* 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:RCo 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:RCo/mg protein.
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 for an individual patient on the use of home treatment of bleedings in patients with VWD and prophylaxis and treatment of bleedings in patients 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.

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.

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).

*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 FVIII administered is expressed in International Units (IU), which is related to the current WHO standard for FVIII products. FVIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or in IU (relative to an International Standard for FVIII in plasma).

1 IU of FVIII activity is equivalent to that quantity of FVIII in 1 ml of normal human plasma.

On demand treatment

The calculation of the required dose of FVIII is based on the empirical finding that 1 IU FVIII per kg body weight raises the plasma FVIII 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 FVIII 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 FVIII 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:

<table>
<thead>
<tr>
<th>Degree of haemorrhage/ Type of surgical procedure</th>
<th>FVIII level required (% or IU/dl)</th>
<th>Frequency of doses (hours) / Duration of therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early haemarthrosis, muscle bleeding or oral bleeding</td>
<td>20 - 40</td>
<td>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.</td>
</tr>
<tr>
<td>More extensive haemarthrosis, muscle bleeding or haematoma</td>
<td>30 - 60</td>
<td>Repeat infusion every 12 - 24 hours for 3 - 4 days or more until pain and acute disability are resolved.</td>
</tr>
<tr>
<td>Life-threatening haemorrhages</td>
<td>60 - 100</td>
<td>Repeat infusion every 8 - 24 hours until threat is resolved.</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor including tooth extraction</td>
<td>30 - 60</td>
<td>Repeat infusion every 24 hours for at least 1 day, until healing is achieved.</td>
</tr>
<tr>
<td>Major 80 - 100 (pre- and postoperative)</td>
<td></td>
<td>Repeat infusion every 8 - 24 hours until adequate wound healing, then continue therapy for at least another 7 days to maintain a FVIII activity of 30 % - 60 % (IU/dl).</td>
</tr>
</tbody>
</table>

During the course of treatment, appropriate determination of FVIII levels is advised to guide the dose to be administered and the frequency of repeated infusions. In the case of major surgical interventions in particular, a precise monitoring of the substitution therapy by means of coagulation analysis (plasma FVIII activity) is indispensable. Individual patients may vary in their response to FVIII, achieving different levels of in vivo recovery and demonstrating different half-lives.

Prophylaxis
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.

Previously untreated patients
The safety and efficacy of Voncento in previously untreated patients have not yet been established.
**Paediatric population**
Dosing in VWD and haemophilia A in adolescents aged 12 to 18 years old is based on body weight and is therefore generally based on the same guidelines as for adults. The frequency of administration should always be oriented to the clinical effectiveness in the individual case.

The safety and efficacy of Voncento in children < 12 years have not been established. No data are available.

**Older people**
No dose adjustment is necessary for the older people.

**Method of administration**
For intravenous use.
Reconstitute the product as described in 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**

**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.
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.

**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 FVIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the FVIII procoagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma, using the modified assay. The risk of developing inhibitors is correlated to the exposure to factor VIII, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days.

Cases of recurrent inhibitor (low titre) have been observed after switching from one factor VIII product to another in previously treated patients with more than 100 exposure days who have a previous history of inhibitor development. Therefore, it is recommended to monitor all patients carefully for inhibitor occurrence following any product switch.

In general, all patients treated with human coagulation FVIII 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. The management of such patients should be directed by physicians with experience in the care of haemophilia A patients and those with factor VIII inhibitors.

**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

This medicine contains up to 29.5 mg (1.28 mmol) sodium per vial. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction 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 in adults and adolescents 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).

<table>
<thead>
<tr>
<th>MedDRA Standard System Organ Class</th>
<th>Adverse Reaction</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>FVIII inhibition</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>VWF inhibition</td>
<td>Very rare</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity (including tachycardia, chest pain, chest)</td>
<td>Very rare</td>
</tr>
<tr>
<td>Category</td>
<td>Adverse Reaction</td>
<td>Frequency</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>-----------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dysgeusia</td>
<td>Very rare</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Thromboembolic event</td>
<td>Very rare</td>
</tr>
<tr>
<td>General disorders and administration site</td>
<td>Pyrexia</td>
<td>Very rare</td>
</tr>
<tr>
<td>conditions</td>
<td>Headache</td>
<td>Very rare</td>
</tr>
<tr>
<td>Investigations</td>
<td>Liver function test</td>
<td>Very rare</td>
</tr>
</tbody>
</table>

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:* Patients with haemophilia A may develop neutralising antibodies (inhibitors) to FVIII. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted. There is no experience from clinical trials with Voncento in previously untreated patients (PUPs). Therefore, no valid figures on the incidence of clinically relevant specific inhibitors are currently available.

*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**

One case of overdose (twice the amount of the recommended dose) has been observed in clinical trials. No severe adverse reactions were associated with this case.

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.

The European Medicines Agency has deferred the obligation to submit the results of studies with Voncento in patients from birth to less than 12 years of age with VWD.

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 haemophilia 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.

The European Medicines Agency has deferred the obligation to submit the results of studies with Voncento in patients from birth to less than 12 years of age with haemophilia A.
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 with VWD, the following pharmacokinetic characteristics for VWF:RCo, VWF:Ag, VWF:CB and FVIII:C were observed:

<table>
<thead>
<tr>
<th>parameter</th>
<th>VWF:RCo</th>
<th>VWF:Ag</th>
<th>VWF:CB</th>
<th>FVIII:C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
<td>SD</td>
<td>range</td>
</tr>
<tr>
<td>Incremental recovery (kg/mL)</td>
<td>12</td>
<td>0.017</td>
<td>0.002</td>
<td>0.01-02</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>8</td>
<td>13.7</td>
<td>9.2</td>
<td>6.1-35.1</td>
</tr>
<tr>
<td>AUC_{0-72} (h*IU/mL)</td>
<td>12</td>
<td>17.7</td>
<td>9.7</td>
<td>12.7-22.7</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>8</td>
<td>14.0</td>
<td>5.0</td>
<td>8.6-25.5</td>
</tr>
<tr>
<td>C_{max} (IU/mL)</td>
<td>12</td>
<td>1.65</td>
<td>0.63</td>
<td>0.93-3.36</td>
</tr>
<tr>
<td>T_{max} (h)</td>
<td>12</td>
<td>0.25*</td>
<td>-</td>
<td>0.25-1.03</td>
</tr>
<tr>
<td>C_{min} (IU/mL)</td>
<td>12</td>
<td>0.01</td>
<td>0.01</td>
<td>0.00-0.03</td>
</tr>
<tr>
<td>Total clearance (mL/(h*kg))</td>
<td>12</td>
<td>6.09</td>
<td>1.66</td>
<td>3.06-9.32</td>
</tr>
<tr>
<td>V_{ss} (ml/kg)</td>
<td>8</td>
<td>74.8</td>
<td>35.3</td>
<td>44.7-158.0</td>
</tr>
</tbody>
</table>

*median

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; SD = standard deviation; t_{max} = time the 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

The relative HMW VWF of Voncento compared to normal human plasma is on average 86%. The relative expression of HMW VWF multimers in VWD patients after infusion of Voncento was approximately 10% (using a semi-quantitative multimer analysis).
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 with haemophilia A, the following pharmacokinetic characteristics for FVIII:C were observed:

<table>
<thead>
<tr>
<th>parameter</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incremental recovery (kg/mL)</td>
<td>16</td>
<td>0.021</td>
<td>0.006</td>
<td>0.011-0.032</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>16</td>
<td>13.40</td>
<td>2.53</td>
<td>8.78-18.51</td>
</tr>
<tr>
<td>AUC_{0-48} (h*IU/mL)</td>
<td>16</td>
<td>13.79</td>
<td>3.79</td>
<td>7.04-21.79</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>16</td>
<td>16.96</td>
<td>3.68</td>
<td>11.29-26.31</td>
</tr>
<tr>
<td>C_{max} (IU/mL)</td>
<td>16</td>
<td>1.07</td>
<td>0.28</td>
<td>0.57-1.57</td>
</tr>
<tr>
<td>T_{max} (h)</td>
<td>16</td>
<td>0.81</td>
<td>0.94</td>
<td>0.42-4.03</td>
</tr>
<tr>
<td>C_{min} (IU/mL)</td>
<td>16</td>
<td>0.060</td>
<td>0.028</td>
<td>0.021-0.111</td>
</tr>
<tr>
<td>Total clearance (mL/(h*kg))</td>
<td>16</td>
<td>3.92</td>
<td>1.22</td>
<td>2.30-7.11</td>
</tr>
<tr>
<td>V_{ss} (ml/kg)</td>
<td>16</td>
<td>65.33</td>
<td>20.65</td>
<td>35.07-113.06</td>
</tr>
</tbody>
</table>

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; SD = standard deviation; T_{max} = time the maximum concentration occurs; V_{ss} = volume of distribution at steady state; FVIII:C = Factor VIII:Coagulant

Paediatric population

No pharmacokinetic data are available in patients younger than 12 years.

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.

After reconstitution the 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 and would normally not be longer than 24 hours at 2 to 8 °C.

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

Immediate containers

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).

Presentation

Pack with 1000 IU/2400 IU:
1 powder vial
1 solvent vial

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 aseptic solution and allowed to dry prior to opening the Mix2Vial package.

1. Open the Mix2Vial package by peeling off the lid. Do not remove the Mix2Vial from the blister package!

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. 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. Place the powder 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. 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 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. Gently swirl the product vial with the transparent adapter attached until the substance is fully dissolved. Do not shake.
Withdrawal and application

7. Draw air into an empty, sterile syringe. While the product vial is upright, connect the syringe to the Mix2Vial’s Luer Lock fitting. Inject air into the product vial.

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. 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.

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 drugs). However, in these cases the initially reconstituted solution of Voncento should not be diluted any further.

Administer 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/1/13/857/004

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorisation: 12 August 2013

10. DATE OF REVISION OF THE TEXT

November 2014

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 / 600 IU
powder and solvent for solution for injection/infusion

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

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

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.
<p>| 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 AUTHORIZATION HOLDER |
| | CSL Behring GmbH, 35041 Marburg, Germany |
| 12. | MARKETING AUTHORIZATION NUMBER(S) |
| | EU/1/13/857/001 |
| 13. | BATCH NUMBER |
| | Lot |
| 14. | GENERAL CLASSIFICATION FOR SUPPLY |
| | Medicinal product subject to medical prescription. |
| 15. | INSTRUCTIONS ON USE |
| 16. | INFORMATION IN BRAILLE |
| | Voncento 250 IU / 600 IU |</p>
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS (Powder vial 250 IU/600 IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</strong></td>
</tr>
</tbody>
</table>
| Voncento 250 IU / 600 IU  
Powder for solution for injection/infusion  
For i.v. 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 / 1200 IU  
   powder and solvent for solution for injection/infusion

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

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

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.
<table>
<thead>
<tr>
<th>10.</th>
<th>SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.</td>
<td>NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</td>
</tr>
<tr>
<td></td>
<td>CSL Behring GmbH, 35041 Marburg, Germany</td>
</tr>
<tr>
<td>12.</td>
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<tr>
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<td>BATCH NUMBER</td>
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<td>Lot</td>
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<tr>
<td>14.</td>
<td>GENERAL CLASSIFICATION FOR SUPPLY</td>
</tr>
<tr>
<td></td>
<td>Medicinal product subject to medical prescription.</td>
</tr>
<tr>
<td>15.</td>
<td>INSTRUCTIONS ON USE</td>
</tr>
<tr>
<td>16.</td>
<td>INFORMATION IN BRAILLE</td>
</tr>
<tr>
<td></td>
<td>Voncento 500 IU / 1200 IU</td>
</tr>
<tr>
<td>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS (Powder vial 500 IU/1200 IU)</td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</td>
<td></td>
</tr>
<tr>
<td>Voncento 500 IU /1200 IU</td>
<td></td>
</tr>
<tr>
<td>Powder for solution for injection/infusion</td>
<td></td>
</tr>
<tr>
<td>For i.v. use</td>
<td></td>
</tr>
<tr>
<td>2. METHOD OF ADMINISTRATION</td>
<td></td>
</tr>
<tr>
<td>3. EXPIRY DATE</td>
<td></td>
</tr>
<tr>
<td>EXP</td>
<td></td>
</tr>
<tr>
<td>4. BATCH NUMBER</td>
<td></td>
</tr>
<tr>
<td>Lot</td>
<td></td>
</tr>
<tr>
<td>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</td>
<td></td>
</tr>
<tr>
<td>coagulation factor VIII 500 IU</td>
<td></td>
</tr>
<tr>
<td>von Willebrand factor 1200 IU</td>
<td></td>
</tr>
<tr>
<td>6. OTHER</td>
<td></td>
</tr>
<tr>
<td>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS (Solvent vial label 10 ml)</td>
<td></td>
</tr>
<tr>
<td>1. <strong>NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</strong></td>
<td></td>
</tr>
<tr>
<td>Water for injections</td>
<td></td>
</tr>
<tr>
<td>2. <strong>METHOD OF ADMINISTRATION</strong></td>
<td></td>
</tr>
<tr>
<td>3. <strong>EXPIRY DATE</strong></td>
<td></td>
</tr>
<tr>
<td>EXP</td>
<td></td>
</tr>
<tr>
<td>4. <strong>BATCH NUMBER</strong></td>
<td></td>
</tr>
<tr>
<td>Lot</td>
<td></td>
</tr>
<tr>
<td>5. <strong>CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</strong></td>
<td></td>
</tr>
<tr>
<td>10 ml</td>
<td></td>
</tr>
<tr>
<td>6. <strong>OTHER</strong></td>
<td></td>
</tr>
</tbody>
</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
(Carton 500 IU/1200 IU)

1. NAME OF THE MEDICINAL PRODUCT
Voncento 500 IU / 1200 IU
powder and solvent for solution for injection/infusion

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

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

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

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Voncento 500 IU / 1200 IU
| MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS  
(Powder vial 500 IU/1200 IU) |
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.  NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</strong></td>
</tr>
</tbody>
</table>
| Voncento 500 IU / 1200 IU  
Powder for solution for injection/infusion  
For i.v. 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 / 2400 IU
powder and solvent for solution for injection/infusion

### 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

### 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

### 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

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Voncento 1000 IU / 2400 IU
**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**  
(Powder vial 1000 IU/2400 IU)

<table>
<thead>
<tr>
<th><strong>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</strong></th>
</tr>
</thead>
</table>
| Voncento 1000 IU / 2400 IU  
Powder for solution for injection/infusion  
For i.v. use |

<table>
<thead>
<tr>
<th><strong>2. METHOD OF ADMINISTRATION</strong></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>3. EXPIRY DATE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
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</table>

<table>
<thead>
<tr>
<th><strong>4. BATCH NUMBER</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lot</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</strong></th>
</tr>
</thead>
</table>
| coagulation factor VIII 1000 IU  
von Willebrand factor 2400 IU |

<table>
<thead>
<tr>
<th><strong>6. OTHER</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</strong></td>
</tr>
<tr>
<td>Water for injections</td>
</tr>
<tr>
<td><strong>2. METHOD OF ADMINISTRATION</strong></td>
</tr>
<tr>
<td><strong>3. EXPIRY DATE</strong></td>
</tr>
<tr>
<td>EXP</td>
</tr>
<tr>
<td><strong>4. BATCH NUMBER</strong></td>
</tr>
<tr>
<td>Lot</td>
</tr>
<tr>
<td><strong>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</strong></td>
</tr>
<tr>
<td>10 ml</td>
</tr>
<tr>
<td><strong>6. OTHER</strong></td>
</tr>
</tbody>
</table>
B. PACKAGE LEAFLET
This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor, your nurse or your pharmacist.
- If 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
2. What you need to know before you use Voncento
3. How to use Voncento
4. Possible side effects
5. How to store Voncento
6. Contents of the pack and other information

1. What Voncento is and what it is used for

What is Voncento and what is it 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 to prevent or to halt bleeding caused by the lack of VWF in von Willebrand disease and the lack of FVIII in haemophilia A. Voncento is only used when treatment with another medicine, desmopressin (DDAVP), 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

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, which stops the treatment working properly. If your bleeding is not being controlled with Voncento, tell your doctor immediately. You should be monitored carefully for the development of inhibitors.

- 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.
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.

**Children and adolescents**

Voncento has not been studied in children under the age of 12 years so far. Therefore, Voncento is not recommended to be used in children under the age of 12 years.

**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**

Voncento contains up to 14.75 mg (0.64 mmol) sodium per vial. Please take this into account if you are on a controlled sodium diet.

3. **How to use Voncento**

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

In case your doctor thinks you could take Voncento on your own, 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**
The dose in VWD and haemophilia A in adolescents aged 12 to 18 years old is based on body weight and worked out in the same way as for adults.
If you use more Voncento than you should
One case of overdose (twice the amount of the recommended dose) has been observed in clinical trials. No severe side effects were associated with this case. 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 °C).

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.

<table>
<thead>
<tr>
<th></th>
<th>1. Open the Mix2Vial package by peeling off the lid. Do not remove the Mix2Vial from the blister package!</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>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.</td>
</tr>
</tbody>
</table>
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. Place the powder vial on an even and firm surface. Turn the solvent vial upside down 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. With one hand grasp the product-side of the Mix2Vial set. With the other hand grasp the solvent-side and unscrew the set carefully 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. Gently swirl the product vial with the transparent adapter attached until the substance is fully dissolved. Do not shake.

7. Draw air into an empty, sterile syringe. While the product vial is upright, connect the syringe to the Mix2Vial’s Luer Lock fitting. Inject air into the product vial.

**Withdrawal and Application**

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. 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.

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 in case of emergency:**
- if you notice symptoms of allergic reactions (see below)
- if you notice that the medicine stops working properly
- if 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)

The following side effects have been observed **very rarely** (may affect up to 1 in 10,000 people):
- **Allergic reactions** have been observed and may in some cases 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. If this happens, you should stop using the medicine immediately and contact your doctor.
- **FVIII/VWF inhibition**: the medicine stops working properly (continuous bleeding). You may develop an inhibitor (neutralising antibody) to FVIII/VWF, in which case FVIII/VWF will not work properly any more. If this happens, you should stop using the medicine immediately and contact your doctor.
- There is a risk of formation of blood clots (thrombosis), particularly in patients with known risk factors (see also section 2).
- Increase in body temperature
- Abnormal liver function test
• Taste alteration (dysgeusia)
• Headache

Side effects in children and adolescents

Side effects in children 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.
• The reconstituted product should preferably be used immediately.
• If the reconstituted product is not administered immediately, storage times and conditions prior to use are the responsibility of the the user and should not exceed 24 hours at 2 to 8 °C.
• Keep the vial in the outer carton in order to protect from light.

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.
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 last paragraph of section 2.
Solvent: Water for injections

What Voncento looks like and contents of the pack

Voncento is presented as a white powder and is supplied with water for injection as solvent.
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.

Presentation
One pack with 250 IU/600 IU containing:
- 1 vial with powder
- 1 vial with 5 ml water for injections
For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

- **België/Belgique/Belgien**
  CSL Behring NV
  Tél/Tel: +32 16 38 80 80

- **България**
  Новимед ООД
  Тел: +359 2 850 8617

- **Česká republika**
  CSL Behring s.r.o.
  Tel: +420 241 416 442

- **Danmark**
  CSL Behring AB
  Tel: +46 8 544 966 70

- **Deutschland**
  CSL Behring GmbH
  Tel: +49 69 30584437

- **Eesti**
  CSL Behring AB
  Tel: +46 8 544 966 70

- **Ελλάδα**
  CSL Behring ΜΕΠΕ
  Τηλ: +30 210 7255 660

- **España**
  CSL Behring S.A.
  Tel: +34 933 67 1870

- **France**
  CSL Behring S.A.
  Tél: +33 –(0)-1 53 58 54 00

- **Hrvatska**
  PharmaSwiss d.o.o.
  Tel: +385 (1) 631-1833

- **Ireland**
  CSL Behring UK Ltd.
  Tel: +44 1444 447405

- **Lietuva**
  CSL Behring AB
  Tel: +46 8 544 966 70

- **Литва**
  CSL Behring Kft.
  Tel.: +36 1 213 4290

- **Luxembourg/Luxemburg**
  CSL Behring NV
  Tél/Tel: +32 16 38 80 80

- **Malta**
  AM Mangion Ltd.
  Tel: +356 2397 6333

- **Nederland**
  CSL Behring BV
  Tel: +31 85 111 96 00

- **Норвегия**
  CSL Behring AB
  Tlf: +46 8 544 966 70

- **Österreich**
  CSL Behring GmbH
  Tel: +43 1 80101 2463

- **Польша**
  Imed Poland Sp.z o.o.
  Tel: +48 22 663 43 10

- **Румыния**
  Prisum International Trading srl
  Tel: +40 21 322 0171

- **Slovenija**
  MediSanus d.o.o.
  Tel: +386 1 25 71 496
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.

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.
**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 FVIII administered is expressed in International Units (IU), which is related to the current WHO standard for FVIII products. FVIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or in IU (relative to an International Standard for FVIII in plasma).

1 IU of FVIII activity is equivalent to that quantity of FVIII in 1 ml of normal human plasma.

**On demand treatment**

The calculation of the required dose of FVIII is based on the empirical finding that 1 IU FVIII per kg body weight raises the plasma FVIII activity by about 2 % of normal activity (in vivo recovery 2 IU/dl). The required dose is determined using the following formula:

\[
\text{Required units} = \text{body weight} \times \text{desired FVIII rise [\% or IU/dl]} \times 0.5.
\]

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 FVIII 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:

<table>
<thead>
<tr>
<th>Degree of haemorrhage / Type of surgical procedure</th>
<th>Factor VIII level required (% or IU/dl)</th>
<th>Frequency of doses (hours) / Duration of therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early haemarthrosis, muscle bleeding or oral bleeding</td>
<td>20 - 40</td>
<td>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.</td>
</tr>
<tr>
<td>More extensive haemarthrosis, muscle bleeding or haematoma</td>
<td>30 - 60</td>
<td>Repeat infusion every 12-24 hours for 3 - 4 days or more until pain and acute disability are resolved.</td>
</tr>
<tr>
<td>Life-threatening haemorrhages:</td>
<td>60 - 100</td>
<td>Repeat infusion every 8 to 24 hours until threat is resolved.</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor including tooth extraction</td>
<td>30 - 60</td>
<td>Repeat infusion every 24 hours for at least 1 day, until healing is achieved.</td>
</tr>
<tr>
<td>Major (pre- and postoperative)</td>
<td>80 - 100</td>
<td>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)</td>
</tr>
</tbody>
</table>

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During the course of treatment, appropriate determination of FVIII levels is advised to guide the dose to be administered and the frequency of repeated infusions. In the case of major surgical interventions in particular, a precise monitoring of the substitution therapy by means of coagulation analysis (plasma FVIII activity) is indispensable. Individual patients may vary in their response to FVIII, achieving different levels of \textit{in vivo} recovery and demonstrating different half-lives.

\textbf{Prophylaxis}
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.

\textbf{Previously untreated patients}
The safety and efficacy of Voncento in previously untreated patients have not yet been established.

\textbf{Paediatric population}
Dosing in VWD and haemophilia A in adolescents aged from 12 to less than 18 years is based on body weight and is therefore generally based on the same guidelines as for adults. The frequency of administration should always be oriented to the clinical effectiveness in the individual case.

The safety and efficacy of Voncento in children < 12 years have not been established. No data are available.

\textbf{Older people}
No dose adjustment is necessary for the older people.
This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4. for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have 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:
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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 to prevent or to halt bleeding caused by the lack of VWF in von Willebrand disease and the lack of FVIII in haemophilia A. Voncento is only used when treatment with another medicine, desmopressin (DDAVP), 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

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, which stops the treatment working properly. If your bleeding is not being controlled with Voncento, tell your doctor immediately. You should be monitored carefully for the development of inhibitors.
- 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.
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.

**Children and adolescents**

Voncento has not been studied in children under the age of 12 years so far. Therefore, Voncento is not recommended to be used in children under the age of 12 years.

**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**

Voncento contains up to 29.50 mg (1.28 mmol) sodium per vial. Please take this into account if you are on a controlled sodium diet.

### 3. How to use Voncento

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

In case your doctor thinks you could take Voncento on your own, 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**

The dose in VWD and haemophilia A in adolescents aged 12 to 18 years old is based on body weight and worked out in the same way as for adults.
If you use more Voncento than you should
One case of overdose (twice the amount of the recommended dose) has been observed in clinical trials. No severe side effects were associated with this case. 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 °C).

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.

<table>
<thead>
<tr>
<th></th>
<th>1. Open the Mix2Vial package by peeling off the lid. Do <strong>not</strong> remove the Mix2Vial from the blister package!</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>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 <strong>straight down</strong> through the solvent vial stopper.</td>
</tr>
</tbody>
</table>
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. Place the powder vial on an even and firm surface. Turn the solvent vial upside down 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. With one hand grasp the product-side of the Mix2Vial set. With the other hand grasp the solvent-side and unscrew the set carefully 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. Gently swirl the product vial with the transparent adapter attached until the substance is fully dissolved. Do not shake.

7. Draw air into an empty, sterile syringe. While the product vial is upright, connect the syringe to the Mix2Vial’s Luer Lock fitting. Inject air into the product vial.

**Withdrawal and Application**

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. 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.

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 in case of emergency:**

- if you notice symptoms of allergic reactions (see below)
- if you notice that the medicine stops working properly
- if 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)

The following side effects have been observed **very rarely** (may affect up to 1 in 10,000 people):

- **Allergic reactions** have been observed and may in some cases 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. If this happens, you should stop using the medicine immediately and contact your doctor.
- **FVIII/VWF inhibition:** the medicine stops working properly (continuous bleeding). You may develop an inhibitor (neutralising antibody) to FVIII/VWF, in which case FVIII/VWF will not work properly any more. If this happens, you should stop using the medicine immediately and contact your doctor.
- There is a risk of formation of blood clots (thrombosis), particularly in patients with known risk factors (see also section 2).
- Increase in body temperature
- Abnormal liver function test
• Taste alteration (dysgeusia)
• Headache

Side effects in children and adolescents

Side effects in children 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 ºC.
• Do not freeze.
• The reconstituted product should preferably be used immediately.
• If the reconstituted product is not administered immediately, storage times and conditions prior to use are the responsibility of the user and should not exceed 24 hours at 2 to 8 ºC.
• Keep the vial in the outer carton in order to protect from light.

6. Contents of the pack and other information

What Voncento contains

The active substance is:
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. 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 last paragraph of section 2.
Solvent: Water for injections

What Voncento looks like and contents of the pack

Voncento is presented as a white powder and is supplied with water for injection as solvent. 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.

Presentation
One pack with 500 IU/1200 IU containing:
- 1 vial with powder
- 1 vial with 10 ml water for injections
**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:

<table>
<thead>
<tr>
<th>Country</th>
<th>Address</th>
<th>Contact Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>België/Belgique/Belgien</td>
<td>CSL Behring NV</td>
<td>Tél/Tel: +32 16 38 80 80</td>
</tr>
<tr>
<td>Lietuva</td>
<td>CSL Behring AB</td>
<td>Tel: +46 8 544 966 70</td>
</tr>
<tr>
<td>България</td>
<td>Новимед ООД</td>
<td>Тел: +359 2 850 8617</td>
</tr>
<tr>
<td>Luxembour/Luxemburg</td>
<td>CSL Behring NV</td>
<td>Tél/Tel: +32 16 38 80 80</td>
</tr>
<tr>
<td>Česká republika</td>
<td>CSL Behring s.r.o.</td>
<td>Tel: +420 241 416 442</td>
</tr>
<tr>
<td>Magyarország</td>
<td>CSL Behring Kft.</td>
<td>Tel.: +36 1 213 4290</td>
</tr>
<tr>
<td>Danmark</td>
<td>CSL Behring AB</td>
<td>Tel: +46 8 544 966 70</td>
</tr>
<tr>
<td>Malta</td>
<td>AM Mangion Ltd.</td>
<td>Tel: +356 2397 6333</td>
</tr>
<tr>
<td>Deutschland</td>
<td>CSL Behring GmbH</td>
<td>Tel: +49 69 30584437</td>
</tr>
<tr>
<td>Nederland</td>
<td>CSL Behring BV</td>
<td>Tel: +31 85 111 96 00</td>
</tr>
<tr>
<td>Eesti</td>
<td>CSL Behring AB</td>
<td>Tel: +46 8 544 966 70</td>
</tr>
<tr>
<td>Norge</td>
<td>CSL Behring AB</td>
<td>Tlf: +46 8 544 966 70</td>
</tr>
<tr>
<td>Elláda</td>
<td>CSL Behring ΜΕΠΕ</td>
<td>Τηλ: +30 210 7255 660</td>
</tr>
<tr>
<td>Österreich</td>
<td>CSL Behring GmbH</td>
<td>Tel: +43 1 80101 2463</td>
</tr>
<tr>
<td>España</td>
<td>CSL Behring S.A.</td>
<td>Tel: +34 933 67 1870</td>
</tr>
<tr>
<td>Polska</td>
<td>Imed Poland Sp.z o.o.</td>
<td>Tel: +48 22 663 43 10</td>
</tr>
<tr>
<td>France</td>
<td>CSL Behring S.A.</td>
<td>Tél: +33 –(0)-1 53 58 54 00</td>
</tr>
<tr>
<td>Portugal</td>
<td>CSL Behring Lda</td>
<td>Tel: +351 21 782 62 30</td>
</tr>
<tr>
<td>Hrvatska</td>
<td>PharmaSwiss d.o.o.</td>
<td>Tel: +385 (1) 631-1833</td>
</tr>
<tr>
<td>România</td>
<td>Prism International Trading srl</td>
<td>Tel: +40 21 322 0171</td>
</tr>
<tr>
<td>Ireland</td>
<td>CSL Behring UK Ltd.</td>
<td>Tel: +44 1444 447405</td>
</tr>
<tr>
<td>Slovenija</td>
<td>MediSanus d.o.o.</td>
<td>Tel: +386 1 25 71 496</td>
</tr>
</tbody>
</table>
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.

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.
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 FVIII administered is expressed in International Units (IU), which is related to the current WHO standard for FVIII products. FVIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or in IU (relative to an International Standard for FVIII in plasma).

1 IU of FVIII activity is equivalent to that quantity of FVIII in 1 ml of normal human plasma.

On demand treatment
The calculation of the required dose of FVIII is based on the empirical finding that 1 IU FVIII per kg body weight raises the plasma FVIII 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 FVIII 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 FVIII 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:

<table>
<thead>
<tr>
<th>Degree of haemorrhage / Type of surgical procedure</th>
<th>Factor VIII level required (% or IU/dl)</th>
<th>Frequency of doses (hours) / Duration of therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early haemarthrosis, muscle bleeding or oral bleeding</td>
<td>20 - 40</td>
<td>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.</td>
</tr>
<tr>
<td>More extensive haemarthrosis, muscle bleeding or haematoma</td>
<td>30 - 60</td>
<td>Repeat infusion every 12-24 hours for 3 - 4 days or more until pain and acute disability are resolved.</td>
</tr>
<tr>
<td>Life-threatening haemorrhages:</td>
<td>60 - 100</td>
<td>Repeat infusion every 8 to 24 hours until threat is resolved.</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor including tooth extraction</td>
<td>30 - 60</td>
<td>Repeat infusion every 24 hours for at least 1 day, until healing is achieved.</td>
</tr>
<tr>
<td>Major (pre- and postoperative)</td>
<td>80 - 100</td>
<td>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)</td>
</tr>
</tbody>
</table>
During the course of treatment, appropriate determination of FVIII levels is advised to guide the dose to be administered and the frequency of repeated infusions. In the case of major surgical interventions in particular, a precise monitoring of the substitution therapy by means of coagulation analysis (plasma FVIII activity) is indispensable. Individual patients may vary in their response to FVIII, achieving different levels of \textit{in vivo} recovery and demonstrating different half-lives.

**Prophylaxis**
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.

**Previously untreated patients**
The safety and efficacy of Voncento in previously untreated patients have not yet been established.

**Paediatric population**
Dosing in VWD and haemophilia A in adolescents aged from 12 to less than 18 years is based on body weight and is therefore generally based on the same guidelines as for adults. The frequency of administration should always be oriented to the clinical effectiveness in the individual case.

The safety and efficacy of Voncento in children < 12 years have not been established. No data are available.

**Older people**
No dose adjustment is necessary for the older people.
This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4. for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have 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
2. What you need to know before you use Voncento
3. How to use Voncento
4. Possible side effects
5. How to store Voncento
6. Contents of the pack and other information

1. What Voncento is and what it is used for

What is Voncento and what is it 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 to prevent or to halt bleeding caused by the lack of VWF in von Willebrand disease and the lack of FVIII in haemophilia A. Voncento is only used when treatment with another medicine, desmopressin (DDAVP), 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

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 which stops the treatment working properly. If your bleeding is not being controlled with Voncento, tell your doctor immediately. You should be monitored carefully for the development of inhibitors.
- 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.

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.

**Children and adolescents**

Voncento has not been studied in children under the age of 12 years so far. Therefore, Voncento is not recommended to be used in children under the age of 12 years.

**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**

Voncento contains up to 14.75 mg (0.64 mmol) sodium per vial. Please take this into account if you are on a controlled sodium diet.

**3. How to use Voncento**

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

In case your doctor thinks you could take Voncento on your own, 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**

The dose in VWD and haemophilia A in adolescents aged 12 to 18 years old is based on body weight and worked out in the same way as for adults.
If you use more Voncento than you should
One case of overdose (twice the amount of the recommended dose) has been observed in clinical trials. No severe side effects were associated with this case. 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.

<table>
<thead>
<tr>
<th>Step</th>
<th>Instruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1. Open the Mix2Vial package by peeling off the lid. Do <strong>not</strong> remove the Mix2Vial from the blister package!</td>
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<tr>
<td>2</td>
<td>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 <strong>straight down</strong> through the solvent vial stopper.</td>
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</table>
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. Place the powder vial on an even and firm surface. Turn the solvent vial upside down 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. With one hand grasp the product-side of the Mix2Vial set. With the other hand grasp the solvent-side and unscrew the set carefully 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. Gently swirl the product vial with the transparent adapter attached until the substance is fully dissolved. Do not shake.

7. Draw air into an empty, sterile syringe. While the product vial is upright, connect the syringe to the Mix2Vial’s Luer Lock fitting. Inject air into the product vial.

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.

Withdrawal and Application
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.

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 in case of emergency:**
- if you notice symptoms of allergic reactions (see below)
- if you notice that the medicine stops working properly
- if 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)

The following side effects have been observed *very rarely* (may affect up to 1 in 10,000 people):
- **Allergic reactions** have been observed and may in some cases 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. If this happens, you should stop using the medicine immediately and contact your doctor.
- **FVIII/VWF inhibition**: the medicine stops working properly (continuous bleeding). You may develop an inhibitor (neutralising antibody) to FVIII/VWF, in which case FVIII/VWF will not work properly any more. If this happens, you should stop using the medicine immediately and contact your doctor.
- There is a risk of formation of blood clots (thrombosis), particularly in patients with known risk factors (see also section 2).
- Increase in body temperature
- Abnormal liver function test
- Taste alteration (dysgeusia)
- Headache

**Side effects in children and adolescents**

Side effects in children 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.
- The reconstituted product should preferably be used immediately.
- If the reconstituted product is not administered immediately, storage times and conditions prior to use are the responsibility of the user and should not exceed 24 hours at 2 to 8 °C.
- Keep the vial in the outer carton in order to protect from light.

6. **Contents of the pack and other information**

**What Voncento contains**

The active substance is:

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.

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 last paragraph of section 2.

Solvent: Water for injections

**What Voncento looks like and contents of the pack**

Voncento is presented as a white powder and is supplied with water for injection as solvent. 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.

**Presentation**

One pack with 500 IU/1200 IU containing:

- 1 vial with powder
- 1 vial with 5 ml water for injections
### 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:

<table>
<thead>
<tr>
<th>Country</th>
<th>Contact Information</th>
</tr>
</thead>
</table>
| België/Belgique/Belgien | CSL Behring NV  
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This leaflet was last revised in 11/2014.

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.

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.
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 FVIII administered is expressed in International Units (IU), which is related to the current WHO standard for FVIII products. FVIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or in IU (relative to an International Standard for FVIII in plasma).

1 IU of FVIII activity is equivalent to that quantity of FVIII in 1 ml of normal human plasma.

On demand treatment

The calculation of the required dose of FVIII is based on the empirical finding that 1 IU FVIII per kg body weight raises the plasma FVIII 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 FVIII 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 FVIII 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:

<table>
<thead>
<tr>
<th>Degree of haemorrhage / Type of surgical procedure</th>
<th>Factor VIII level required (% or IU/dl)</th>
<th>Frequency of doses (hours) / Duration of therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early haemarthrosis, muscle bleeding or oral bleeding</td>
<td>20 - 40</td>
<td>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.</td>
</tr>
<tr>
<td>More extensive haemarthrosis, muscle bleeding or haematoma</td>
<td>30 - 60</td>
<td>Repeat infusion every 12-24 hours for 3 - 4 days or more until pain and acute disability are resolved.</td>
</tr>
<tr>
<td>Life-threatening haemorrhages:</td>
<td>60 - 100</td>
<td>Repeat infusion every 8 to 24 hours until threat is resolved.</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor including tooth extraction</td>
<td>30 - 60</td>
<td>Repeat infusion every 24 hours for at least 1 day, until healing is achieved.</td>
</tr>
<tr>
<td>Major</td>
<td>80 - 100 (pre- and postoperative)</td>
<td>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)</td>
</tr>
</tbody>
</table>
During the course of treatment, appropriate determination of FVIII levels is advised to guide the dose to be administered and the frequency of repeated infusions. In the case of major surgical interventions in particular, a precise monitoring of the substitution therapy by means of coagulation analysis (plasma FVIII activity) is indispensable. Individual patients may vary in their response to FVIII, achieving different levels of \textit{in vivo} recovery and demonstrating different half-lives.

Prophylaxis
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.

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

Paediatric population
Dosing in VWD and haemophilia A in adolescents aged from 12 to less than 18 years is based on body weight and is therefore generally based on the same guidelines as for adults. The frequency of administration should always be oriented to the clinical effectiveness in the individual case.

The safety and efficacy of Voncento in children < 12 years have not been established. No data are available.

Older people
No dose adjustment is necessary for the older people.
This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have 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
2. What you need to know before you use Voncento
3. How to use Voncento
4. Possible side effects
5. How to store Voncento
6. Contents of the pack and other information

1. What Voncento is and what it is used for

What is Voncento and what is it 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 to prevent or to halt bleeding caused by the lack of VWF in von Willebrand disease and the lack of FVIII in haemophilia A. Voncento is only used when treatment with another medicine, desmopressin (DDAVP), 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**

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 which stops the treatment working properly. If your bleeding is not being controlled with Voncento, tell your doctor immediately. You should be monitored carefully for the development of inhibitors.
- 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.

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

**Children and adolescents**

Voncento has not been studied in children under the age of 12 years so far. Therefore, Voncento is not recommended to be used in children under the age of 12 years.

**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**

Voncento contains up to 29.5 mg (1.28 mmol) sodium per vial. Please take this into account if you are on a controlled sodium diet.

3. **How to use Voncento**

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

In case your doctor thinks you could take Voncento on your own, 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**

The dose in VWD and haemophilia A in adolescents aged 12 to 18 years old is based on body weight and worked out in the same way as for adults.
If you use more Voncento than you should
One case of overdose (twice the amount of the recommended dose) has been observed in clinical trials. No severe side effects were associated with this case. 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. Open the Mix2Vial package by peeling off the lid. Do not remove the Mix2Vial from the blister package!

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. 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. Place the powder vial on an even and firm surface. Turn the solvent vial upside down 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. With one hand grasp the product-side of the Mix2Vial set. With the other hand grasp the solvent-side and unscrew the set carefully 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. Gently swirl the product vial with the transparent adapter attached until the substance is fully dissolved. Do not shake.

7. Draw air into an empty, sterile syringe. While the product vial is upright, connect the syringe to the Mix2Vial’s Luer Lock fitting. Inject air into the product vial.

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. 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.

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 in case of emergency:**
- if you notice symptoms of allergic reactions (see below)
- if you notice that the medicine stops working properly
- if 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)

The following side effects have been observed very rarely (may affect up to 1 in 10,000 people):
- **Allergic reactions** have been observed and may in some cases 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. If this happens, you should stop using the medicine immediately and contact your doctor.
- **FVIII/VWF inhibition**: the medicine stops working properly (continuous bleeding). You may develop an inhibitor (neutralising antibody) to FVIII/VWF, in which case FVIII/VWF will not work properly any more. If this happens, you should stop using the medicine immediately and contact your doctor.
- There is a risk of formation of blood clots (thrombosis), particularly in patients with known risk factors (see also section 2).
- Increase in body temperature
- Abnormal liver function test
- Taste alteration (dysgeusia)
- Headache

**Side effects in children and adolescents**

Side effects in children 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.
- The reconstituted product should preferably be used immediately.
- If the reconstituted product is not administered immediately, storage times and conditions prior to use are the responsibility of the user and should not exceed 24 hours at 2 to 8 °C.
- Keep the vial in the outer carton in order to protect from light.

6. **Contents of the pack and other information**

**What Voncento contains**

The active substance is:
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 last paragraph of section 2.
Solvent: Water for injections

**What Voncento looks like and contents of the pack**

Voncento is presented as a white powder and is supplied with water for injection as solvent. 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.

**Presentation**
One pack with 1000 IU/2400 IU containing:
- 1 vial with powder
- 1 vial with 10 ml water for injections
Marketing Authorization Holder and Manufacturer

CSL Behring GmbH
Emil-von-Behring-Straße 76
35041 Marburg
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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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.

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.
### 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 FVIII administered is expressed in International Units (IU), which is related to the current WHO standard for FVIII products. FVIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or in IU (relative to an International Standard for FVIII in plasma).

1 IU of FVIII activity is equivalent to that quantity of FVIII in 1 ml of normal human plasma.

#### On demand treatment

The calculation of the required dose of FVIII is based on the empirical finding that 1 IU FVIII per kg body weight raises the plasma FVIII activity by about 2% of normal activity (*in vivo recovery* 2 IU/dl). The required dose is determined using the following formula:

\[
\text{Required units} = \text{body weight [kg]} \times \text{desired FVIII rise [% or IU/dl]} \times 0.5.
\]

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 FVIII 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:

<table>
<thead>
<tr>
<th>Degree of haemorrhage / Type of surgical procedure</th>
<th>Factor VIII level required (% or IU/dl)</th>
<th>Frequency of doses (hours) / Duration of therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemorrhage</td>
<td></td>
<td></td>
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<tr>
<td>Early haemarthrosis, muscle bleeding or oral bleeding</td>
<td>20 - 40</td>
<td>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.</td>
</tr>
<tr>
<td>More extensive haemarthrosis, muscle bleeding or haematoma</td>
<td>30 - 60</td>
<td>Repeat infusion every 12-24 hours for 3 - 4 days or more until pain and acute disability are resolved.</td>
</tr>
<tr>
<td>Life-threatening haemorrhages:</td>
<td>60 - 100</td>
<td>Repeat infusion every 8 to 24 hours until threat is resolved.</td>
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<tr>
<td>Surgery</td>
<td></td>
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<tr>
<td>Minor including tooth extraction</td>
<td>30 - 60</td>
<td>Repeat infusion every 24 hours for at least 1 day, until healing is achieved.</td>
</tr>
<tr>
<td>Major (pre- and postoperative)</td>
<td>80 - 100</td>
<td>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)</td>
</tr>
</tbody>
</table>

During the course of treatment, appropriate determination of FVIII levels is advised to guide the dose to be administered and the frequency of repeated infusions. In the case of major surgical interventions...
in particular, a precise monitoring of the substitution therapy by means of coagulation analysis (plasma FVIII activity) is indispensable. Individual patients may vary in their response to FVIII, achieving different levels of \textit{in vivo} recovery and demonstrating different half-lives.

Prophylaxis
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.

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

\textbf{Paediatric population}
Dosing in VWD and haemophilia A in adolescents aged from 12 to less than 18 years is based on body weight and is therefore generally based on the same guidelines as for adults. The frequency of administration should always be oriented to the clinical effectiveness in the individual case.

The safety and efficacy of Voncento in children < 12 years have not been established. No data are available.

\textbf{Older people}
No dose adjustment is necessary for the older people.