

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

VEYVONDI 650 IU powder and solvent for solution for injection.
VEYVONDI 1300 IU powder and solvent for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VEYVONDI 650 IU powder and solvent for solution for injection

Each vial of powder contains nominally 650 International Units (IU) vonicog alfa.
After reconstitution with the 5 mL solvent provided, VEYVONDI contains approximately 130 IU/mL vonicog alfa.

VEYVONDI 1300 IU powder and solvent for solution for injection

Each vial of powder contains nominally 1300 International Units (IU) vonicog alfa.
After reconstitution with the 10 mL solvent provided, VEYVONDI contains approximately 130 IU/mL vonicog alfa

The specific activity of VEYVONDI is approximately 110 IU VWF:RCo/mg protein.

The potency of VWF (IU) is measured using the European Pharmacopoeia ristocetin cofactor activity assay (VWF: RCo). The ristocetin cofactor activity of recombinant human von Willebrand factor was determined against the International Standard for von Willebrand factor concentrate (WHO).

Vonicog alfa is a purified recombinant human von Willebrand factor (rVWF). It is manufactured by recombinant DNA (rDNA) technology in the Chinese Hamster Ovary (CHO) cell line without the addition of any exogenous human-or animal-derived protein in the cell culture process, purification or final formulation.

The product contains only trace amounts of human recombinant coagulation factor VIII (≤ 0.01 IU FVIII / IU VWF: RCo) as determined using the European Pharmacopoeia chromogenic assay for factor VIII (FVIII).

Excipient(s) with known effect

Each 650 IU powder vial contains 5.2 mg sodium.

Each 1300 IU powder vial contains 10.4 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

The powder is a white to off-white lyophilized powder
The solvent is a clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VEYVONDI is indicated in adults (age 18 and older) with von Willebrand Disease (VWD), when desmopressin (DDAVP) treatment alone is ineffective or not indicated for the

- Treatment of haemorrhage and surgical bleeding
- Prevention of surgical bleeding.

VEYVONDI should not be used in the treatment of Haemophilia A.

4.2 Posology and method of administration

Treatment of von Willebrand disease (VWD) should be supervised by a physician experienced in the treatment of haemostatic disorders.

Posology

Dosage and frequency of administration must be individualized according to clinical judgement and based on the patient's weight, type and severity of the bleeding episodes/surgical intervention and based on monitoring of appropriate clinical and laboratory measures. Dose based on bodyweight may require adjustment in underweight or overweight patients.

Generally, 1 IU/kg (VWF:RCo/VEYVONDI/vonicog alfa) raises the plasma VWF:RCo by 0.02 IU/mL (2%).

Haemostasis cannot be ensured until Factor VIII coagulant activity (FVIII:C) is at least 0.4 IU/mL ($\geq 40\%$ of normal activity). Depending on the patient's baseline FVIII:C levels, a single infusion of rVWF will, in a majority of patients, lead to an increase above 40% in endogenous FVIII:C activity within 6 hours and will result in sustaining this level up to 72 hours post infusion. 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. If the patient's baseline plasma FVIII:C level is $< 40\%$ or is unknown and in all situations where a rapid correction of haemostasis should be achieved, such as treatment of an acute haemorrhage, severe trauma or emergency surgery, it is necessary to administer a recombinant factor VIII product with the first infusion of VEYVONDI, in order to achieve a haemostatic plasma level of FVIII:C.

However, if an immediate rise in FVIII:C is not necessary, or if the baseline FVIII:C level is sufficient to ensure haemostasis, the physician may decide to omit the co-administration of rFVIII at the first infusion with VEYVONDI.

In case of major bleeding events or major surgeries requiring repeated, frequent infusions, monitoring of FVIII:C levels is recommended, to decide if rFVIII is required for subsequent infusions to avoid excessive rise of FVIII:C.

Treatment of bleeding episodes (On demand treatment)

Start of treatment

The first dose of VEYVONDI should be 40 to 80 IU/kg body weight. Replacement levels of VWF:RCo > 0.6 IU/mL (60%) and FVIII:C > 0.4 IU/mL (40%) should be achieved. Dosing guidelines for treatment of minor and major haemorrhages are provided in Table 1.

VEYVONDI should be administered with recombinant factor VIII if the FVIII:C levels are $< 40\%$, or are unknown, to control bleeding. The rFVIII dose should be calculated according to the difference between the patient's baseline plasma FVIII:C level, and the desired peak FVIII:C level to achieve an

appropriate plasma FVIII:C level based on the approximate mean recovery of 0.02 (IU/mL)/(IU/kg). The complete dose of VEYVONDI should be administered followed by rFVIII within 10 minutes.

Calculating dose:

$$\text{VEYVONDI dose [IU]} = \text{dose [IU/kg]} \times \text{weight [kg]}$$

Subsequent infusions:

A subsequent dose of 40 IU to 60 IU/kg of VEYVONDI should be infused every 8 to 24 hours as per the dosing ranges in Table 1, or as long as clinically appropriate. In major bleeding episodes, maintain trough levels of VWF:RCo greater than 50% for as long as deemed necessary.

Based on experience from clinical studies, once VWF has been replaced, endogenous FVIII levels will remain normal or near normal as long as VEYVONDI is continued to be administered.

Table 1
Dosing recommendations for the treatment of minor and major haemorrhages

Haemorrhage	Initial dose ^a (IU VWF:RCo/kg body weight)	Subsequent dose
Minor (e.g. epistaxis, oral bleeding, menorrhagia)	40 to 50 IU/kg	40 to 50 IU/kg every 8 to 24 hours (or as long as deemed clinically necessary)
Major ^b (e.g. severe or refractory epistaxis, menorrhagia, gastrointestinal bleeding, central nervous system trauma, haemarthrosis, or traumatic haemorrhage)	50 to 80 IU/kg	40 to 60 IU/kg every 8 to 24 hours for approximately 2-3 days (or as long as deemed clinically necessary)

^aIf rFVIII is administered, see rFVIII package insert for reconstitution and administration instructions.

^bA bleed could be considered major if red blood cell transfusion is either required or potentially indicated or if bleeding occurs in a critical anatomical site (e.g., intracranial or gastrointestinal haemorrhage).

Prevention of bleeding/haemorrhage and treatment in case of elective surgery

Prior to Surgery:

In patients with inadequate levels of FVIII, a dose of 40-60 IU/kg VEYVONDI should be administered 12-24 hours prior to initiating elective surgery (pre-operative dose), to ensure pre-operative endogenous FVIII levels of at least 0.4 IU/mL for minor and at least 0.8 IU/mL for major surgery.

For prevention of excessive bleeding in case of elective surgery, within 3 hours prior to initiation of any surgical procedure, the FVIII:C levels should be assessed. If the FVIII:C levels are at the recommended target level of:

- at least 0.4 IU/mL for minor and oral surgery and
- at least 0.8 IU/mL for major surgery,

a dose of VEYVONDI alone should be administered within 1 hour prior to the procedure.

If the FVIII:C levels are not at the recommended target levels, rFVIII should be administered in addition to vonicog alfa to raise VWF:RCo and FVIII:C, within 1 hour prior to the procedure. Please refer to **Table 2** for FVIII:C recommended target levels. The dose depends on VWF and FVIII levels of the patient, the type and severity of the expected bleeding.

Table 2
Recommended Target Peak Plasma Levels of VWF:RCo and FVIII:C to be Achieved Prior to Surgery for the Prevention of Excessive Bleeding During and After Surgery

Type of Surgery	VWF:RCo Target Peak Plasma Level	FVIII:C Target Peak Plasma Level ^a	Calculation of rVWF dose (to be administered within 1 hour prior to surgery) (IU VWF:RCo required)
Minor	0.50 – 0.60 IU/mL	0.40 – 0.50 IU/mL	Δ^b VWF:RCo x BW (kg) /IR ^c
Major	1 IU/mL	0.80 - 1 IU/mL	Δ^b VWF:RCo x BW (kg) /IR ^c

^a Additional rFVIII may be required to attain the recommended FVIII:C target peak plasma levels. Dosing guidance should be done based on the IR.

^b Δ = Target peak plasma VWF:RCo – baseline plasma VWF:RCo

^c IR = Incremental Recovery as measured in the subject. If the IR is not available, assume an IR of 0.02 IU/mL per IU/kg.

During and After Surgery:

After the initiation of the surgical procedure, the VWF:RCo and FVIII:C plasma levels should be monitored and the intra- and post-operative substitution regimen should be individualised according to the PK results, intensity and duration of the haemostatic challenge, and the institution's standard of care. In general, the frequency of VEYVONDI dosing for post-operative substitution should range from twice a day to every 48 hours. Please refer to Table 3 for treatment recommendations for subsequent maintenance doses.

Table 3
Recommended Target Trough Plasma Levels of VWF:RCo and FVIII:C and Minimum Duration of Treatment for Subsequent Maintenance Doses for the Prevention of Excessive Bleeding After Surgery

Type of Surgery	VWF:RCo Target Trough Plasma Level		FVIII:C Target Trough Plasma Level		Minimum Duration of treatment	Frequency of dosing
	Up to 72 hours post surgery	After 72 hours post surgery	Up to 72 hours post surgery	After 72 hours post surgery		
Minor	≥ 0.30 IU/mL	-	> 0.40 IU/mL	-	48 hours	Every 12-24 hrs / every other day
Major	> 0.50 IU/mL	> 0.30 IU/mL	> 0.50 IU/mL	> 0.40 IU/mL	72 hours	Every 12-24 hrs / every other day

Paediatric population

The safety and efficacy of VEYVONDI in children aged 0 to 18 years have not yet been established. No data are available.

Method of administration

VEYVONDI is for intravenous use. The reconstituted product should be inspected visually prior to administration.

The rate of administration should be slow enough to ensure the comfort of the patient, up to a maximum of 4 mL/min. The patient should be observed for any immediate reaction. If any reaction, such as tachycardia, occurs that might be related to the administration of the product, the rate of infusion should be reduced or stopped as required by the clinical condition of the patient. When co-administration of rVWF and rFVIII is considered necessary, they can be pre-mixed in a single syringe to achieve the appropriate dose. The contents of each vial of rVWF and rFVIII can be drawn into a single syringe by using a separate unused reconstitution device (see section 6.2 for incompatibilities).

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

4.3 Contraindications

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

Known allergic reaction to mouse or hamster proteins.

4.4 Special warnings and precautions for use

In actively bleeding patients it is recommended to co-administer a FVIII product with VEYVONDI as a first line treatment and depending on the FVIII activity levels (see section 4.2).

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity reactions

Hypersensitivity reactions (including anaphylaxis) have occurred. Patients and/or their caregivers should be informed of the early signs of hypersensitivity reactions, which may include but are not limited to tachycardia, tightness of the chest, wheezing and/or acute respiratory distress, hypotension, generalised urticaria, pruritus, rhinoconjunctivitis, angioedema, lethargy, nausea, vomiting, paresthesia, restlessness, and may progress to anaphylactic shock. In case of shock, standard medical treatment for shock should be implemented.

Patients should be closely monitored and carefully observed for any symptoms throughout the infusion period. If signs and symptoms of severe allergic reactions occur, immediately discontinue administration of VEYVONDI and provide appropriate supportive care.

Adequate medical treatment and provisions should be available for immediate use for a potential anaphylactic reaction, especially for patients with a history of allergic reactions.

VEYVONDI contains trace amounts of mouse immunoglobulin G (MuIgG) and Hamster proteins (less than or equal to 2 ng/IU VEYVONDI). Patients treated with this product may develop hypersensitivity reactions to these non-human mammalian proteins. VEYVONDI contains trace amounts of recombinant coagulation factor VIII.

Thrombosis and Embolism

There is a risk of occurrence of thrombotic events, particularly in patients with known clinical or laboratory risk factors for thrombosis including low ADAMTS13 levels. Therefore, patients at risk have to be monitored for early signs of thrombosis, and prophylaxis measures against thromboembolism should be instituted according to current recommendations and standard of care.

In patients requiring frequent doses of VEYVONDI in combination with recombinant factor VIII, plasma levels for FVIII:C activity should be monitored to avoid sustained excessive FVIII:C plasma levels, which may increase the risk of thrombotic events.

Any FVIII that would be administered along with VEYVONDI should be a pure FVIII product. A combination with a FVIII product containing VWF would pose an additional risk of thrombotic events.

Neutralizing antibodies (Inhibitors)

Patients with VWD, especially Type 3, may develop neutralising antibodies (inhibitors) to von Willebrand factor. If the expected plasma levels of (VWF:RCo) are not attained, or if bleeding is not controlled with an appropriate dose, an appropriate assay should be performed to determine if a von

Willebrand factor inhibitor is present. In patients with high levels of anti-VWF antibodies, von Willebrand factor therapy may not be effective and other therapeutic options should be considered.

Treatment of VWD patients who have high-titer binding antibodies (due to previous treatment with pdVWF) may require a higher dose to overcome the binding antibody effect and such patients could be managed clinically by administration of higher doses of vonicog alfa based on the PK data for each individual patient.

Excipient related considerations

This medicinal product contains 5.2 mg sodium in each 650 IU vial or 10.4 mg sodium in each 1300 IU vial. This is equivalent to 2.2% of the WHO recommended maximum daily intake of 2 g sodium for an adult, assuming a body weight of 70 kg and a dose of 80 IU/kg body weight. This is 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 interactions of human von Willebrand factor products with other medicinal products are known.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with VEYVONDI.

Pregnancy

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

Breast-feeding

It is unknown whether VEYVONDI is excreted in human milk. Therefore, VEYVONDI should be administered to lactating von Willebrand factor deficient women only if clearly indicated. Healthcare professionals should balance the potential risks and only prescribe VEYVONDI if needed.

Fertility

The effects of VEYVONDI on fertility have not been established.

4.7 Effects on ability to drive and use machines

VEYVONDI has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

During treatment with VEYVONDI the following adverse reactions may occur:

Hypersensitivity or allergic reactions, thromboembolic events, inhibitor formation against VWF.

Tabulated list of adverse reactions

The table 4 lists the adverse reactions reported in clinical trials, post-authorisation safety studies or post-marketing reporting.

Frequency categories are defined according to the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in the order of decreasing seriousness.

Table 4 Summary of Adverse Reactions reported in Clinical Trials, Post-authorisation safety studies or post-marketing with VEYVONDI in von Willebrand Disease			
MedDRA System Organ Class (SOC)	Adverse Reaction by Preferred Term (PT)	Frequency Category by Subject	Number and Frequency by Subject^a (N=80) n (%)
Nervous system disorders	Dizziness	Common	3 (3.75)
	Vertigo	Common	2 (2.50)
	Dysgeusia	Common	1 (1.25)
	Tremor	Common	1 (1.25)
Cardiac disorders	Tachycardia	Common	1 (1.25)
Vascular disorders	Deep venous thrombosis	Common	1 (1.25)
	Hypertension	Common	1 (1.25)
	Hot flush	Common	1 (1.25)
Gastrointestinal disorders	Vomiting	Common	3 (3.75)
	Nausea	Common	3 (3.75)
Skin and subcutaneous tissue disorders	Pruritus generalized	Common	2 (2.50)
General disorders and administration site conditions	Chest discomfort	Common	1 (1.25)
	Infusion site paraesthesia	Common	1 (1.25)
	Infusion-related reaction (including tachycardia, flushing, rash, dyspnea, blurred vision)	Not known	
Investigations	Electrocardiogram T wave inversion	Common	1 (1.25)
	Heart rate increased	Common	1 (1.25)
Immune system disorders	Anaphylactic reaction	Not known	

^a **Frequency by Subject:** Total number of subjects experiencing the AE (related and unrelated) divided by total number of subjects (N) and multiplied by 100. Not known: cannot be estimated from the available data (observed during post-marketing surveillance).

Description of selected adverse reactions

In clinical trials, one case of clinically asymptomatic deep vein thrombosis (DVT) was reported for a subject in the surgery study who had total hip replacement.

In addition, one post-marketing case of DVT has been reported spontaneously for an elderly patient.

Hypersensitivity

There is a possibility of developing hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, rhinoconjunctivitis, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) which may in some cases progress to anaphylaxis (including shock).

Patients with von Willebrand disease, especially Type 3, may very rarely develop neutralising antibodies (inhibitors) to von Willebrand factor. If such inhibitors occur, the condition may manifest itself as an inadequate clinical response. Such antibodies may occur in close association with hypersensitivity or anaphylactic reactions. Therefore, patients experiencing hypersensitivity or anaphylactic reactions should be tested and evaluated for the presence of an inhibitor.

In all such cases, it is recommended that a specialised haemophilia centre be contacted.

Thrombogenicity

There is a risk of occurrence of thrombotic events, particularly in patients with known clinical or laboratory risk factors including low ADAMTS13 levels. Therefore, patients at risk have to be monitored for early signs of thrombosis, and prophylaxis measures against thromboembolism should be instituted according to current recommendations and standard of care.

Immunogenicity

The immunogenicity of VEYVONDI was assessed in clinical trials by monitoring the development of neutralizing antibodies against VWF and FVIII, as well as binding antibodies against VWF, Furin, Chinese Hamster Ovary (CHO) protein and mouse IgG. No treatment-emergent development of neutralizing antibodies against human VWF or neutralizing antibodies against human rFVIII was observed. One of the 80 subjects who received VEYVONDI peri-operatively in clinical studies developed treatment-emergent binding antibodies against VWF following a surgery for whom no adverse events or lack of haemostatic efficacy has been reported. Binding antibodies against impurities such as rFurin, CHO-protein or mouse IgG were not observed after treatment with VEYVONDI.

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

No symptoms of overdose with von Willebrand factor have been reported. Thromboembolic events may occur in case of major overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihæmorrhagics: blood coagulation factor von Willebrand factor. ATC code: B02BD10

Mechanism of action

VEYVONDI is a recombinant human von Willebrand factor (rVWF). VEYVONDI behaves in the same way as endogenous von Willebrand factor.

Administration of VEYVONDI allows correction of the haemostatic abnormalities exhibited by patients who suffer from von Willebrand factor deficiency (von Willebrand's disease) at two levels:

- VEYVONDI re-establishes platelet adhesion to the vascular sub-endothelium at the site of vascular damage (as it binds both to the vascular sub-endothelium matrix (e.g. collagen) 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.
- VEYVONDI produces delayed correction of the associated factor VIII deficiency. Administered intravenously, VEYVONDI binds to endogenous factor VIII (which is produced normally by the patient), and by stabilising this factor, avoids its rapid degradation. Because of this, administration of VEYVONDI restores the FVIII:C level to normal as a secondary effect after the first infusion. Administration of the FVIII:C rises above 40% within 6 hours and peaks within 24 hours in a majority of patients, depending on the baseline FVIII:C level.

VEYVONDI is a rVWF that contains ultra-large multimers in addition to all of the multimers found in plasma as it is not exposed to proteolysis by ADAMTS13 during the manufacturing process.

Clinical efficacy and safety

The clinical safety, efficacy and PK data were assessed in 3 completed trials, (070701, 071001 and 071101) which enrolled patients with VWD. A total of 92 unique subjects (80 unique subjects with VWD in studies 070701, 071001 and 071101 and 12 subjects with Haemophilia A in study 071104) were exposed to VEYVONDI during clinical development.

The European Medicines Agency has deferred the obligation to submit the results of studies with VEYVONDI in all subsets of the paediatric population in the treatment of von Willebrand Disease (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of VEYVONDI were determined in three clinical studies by assessing the plasma levels of VWF:RCo, von Willebrand Factor Antigen (VWF:Ag), and von Willebrand Collagen Binding Activity (VWF:CB). In all three studies, subjects were evaluated in the non-bleeding state. Sustained increase of FVIII:C was observed by six hours after a single infusion of VEYVONDI.

Table 6 summarizes the PK of VEYVONDI after 50 IU/kg VWR:RCo (PK₅₀) or 80 IU/kg VWF:RCo (PK₈₀) infusions. The mean duration of infusion was 16.5 minutes (SD ± 3.51 minutes) for 50 IU/kg (PK₅₀) and 11.8 minutes (± 2.86 minutes) for 80 IU/kg VWF:RCo (PK₈₀).

Parameter	Phase 1 PK₅₀ VEYVONDI with octocog alfa^g (Study 070701)	Phase 3 PK₅₀ VEYVONDI (Study 071001)	Phase 3 PK₈₀ VEYVONDI (Study 071001)	Surgery PK₅₀ VEYVONDI (Study 071101)
	Mean (95% CI) SD	Mean (95% CI) SD	Mean (95% CI) SD	Mean (95% CI) SD
T_{1/2}^a	19.3 (14.3; 24.3) 10.99	22.6 (19.5; 25.7) 5.34	19.1 (16.7; 21.5) 4.32	17.8 (12.9; 22.8) 7.34
Cl^b	0.04 (0.03; 0.05) 0.028	0.02 (0.02; 0.03) 0.005	0.03 (0.02; 0.03) 0.009	0.03 (0.02; 0.04) 0.011
IR at C_{max}^c	1.7 (1.4; 2.0) 0.62	1.9 (1.6; 2.1) 0.41	2.0 (1.7; 2.2) 0.39	2.0 (1.7; 2.3) 0.45
AUC_{0-inf}^d	1541.4 (1295.7; 1787.2) 554.31	2105.4 (1858.6; 2352.3) 427.51	2939.0 (2533.2; 3344.8) 732.72	1834.4 (1259.0; 2409.7) 856.45
AUC_{0-inf}/Dose^e	33.4 (27.2; 39.5) 13.87	42.1 (37.3; 46.9) 8.31	36.8 (31.8; 41.8) 8.97	37.5 (25.3; 49.7) 18.14

^a[hours], ^b[dL/kg/hours], ^c[(IU/dL)/(U VWF:RCo/kg)] ^d[(h*IU/dL)] ^e[(h*IU/dL)/(IU VWF:RCo/kg)]

^f[VWF:RCo assays with different sensitivity and working ranges were used: Phase 1: automated assay 0.08 – 1.50 IU/mL and sensitive manual assay 0.01 – 0.08 IU/mL; Phase 3: automated assay 0.08 – 1.50 IU/mL

^g This trial was done using ADVATE, a recombinant factor VIII

An exploratory analysis of combined data from studies 070701 and 071001 indicated a statistically significantly (at the 5% level) longer mean residence time, a statistically significantly (at the 5% level) longer terminal half-life and statistically significantly (at the 5% level) larger AUC_{0-inf} regarding VWF:RCo following administration with VEYVONDI (50 IU/kg VWF:RCo) and combined administration of VEYVONDI and octocog alfa (50 IU/kg VWF:RCo and 38.5 IU/kg rFVIII) than after administration of pdVWF and pdFVIII (50 IU/kg pdVWF:RCo and 38.5 IU/kg pdFVIII).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

No investigations on carcinogenicity, fertility impairment and fetal development have been conducted. In a human ex vivo placenta perfusion model, it has been demonstrated that VEYVONDI does not cross the human placenta barrier.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Sodium citrate
Glycine
Trehalose dihydrate
Mannitol
Polysorbate 80

Solvent

Water for injections

6.2 Incompatibilities

Clinical and compatibility studies were conducted to administer vonicog alfa (human von Willebrand factor) with octocog alfa (human coagulation factor) in the same syringe. The rVWF and rFVIII can be pre-mixed in a single syringe to achieve the appropriate dose (see section 4.2 for mode of administration). This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6

6.3 Shelf life

Unopened vial

3 years.

Shelf-life after reconstitution:

Chemical and physical in-use stability has been demonstrated for 3 hours at 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, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Powder

Do not store above 30°C.
Do not freeze.
Store in the original package in order to protect from light.

After reconstitution

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

VEYVONDI 650 IU powder and solvent for solution for injection

Each pack contains:

- powder in a vial (type I glass), with a butyl rubber stopper
- 5 mL of solvent in a vial (type I glass), with a rubber stopper (chlorobutyl)
- one reconstitution device (Mix2Vial)

VEYVONDI 1300 IU powder and solvent for solution for injection

Each pack contains:


- powder in a vial (type I glass), with a butyl rubber stopper
- 10 mL of solvent in a vial (type I glass), with a rubber stopper (bromobutyl)
- one reconstitution device (Mix2Vial)

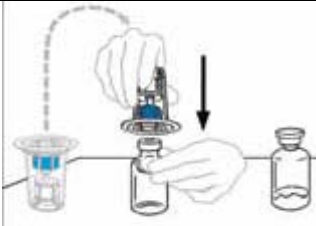
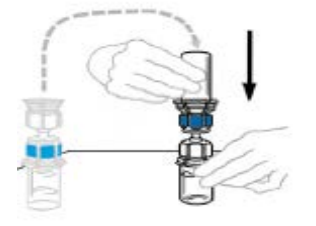

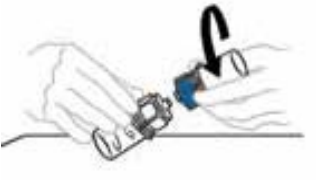
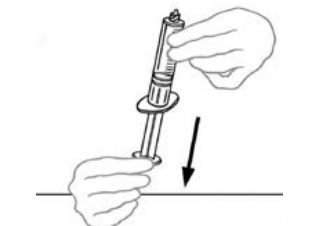

6.6 Special precautions for disposal and other handling

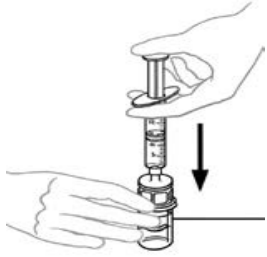
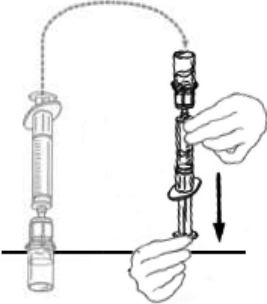

General Instructions

- Check the expiry date, and ensure that the VEYVONDI powder and water for injections (solvent) are at room temperature prior to preparation. Do not use after the expiry date stated on the labels and carton.
- Use antiseptic technique (clean and low-germ conditions) and a flat work surface during the reconstitution procedure. Wash your hands and put on clean exam gloves (the use of gloves is optional).
- Use the reconstituted product (after mixing the powder with the supplied water) as soon as possible and within three hours. You can store the reconstituted product at room temperature not to exceed 25° C for up to three hours.
- Ensure that the VEYVONDI powder vial and the sterilised water for injections (solvent) are at room temperature prior to preparation.
- Use plastic syringes with this product because proteins in the product tend to stick to the surface of glass syringes.
- Do not mix vonicog alfa with other medicinal products except for rFVIII.

Instructions for Reconstitution and application

	Steps	Image example
1	Remove the caps from the VEYVONDI powder and solvent vials to expose the centre of the rubber stoppers.	
2	Disinfect each stopper with a separate sterile alcohol swab (or other suitable sterile solution suggested by your doctor or haemophilia treatment centre) by wiping the stopper for several seconds. Allow the rubber stopper to dry. Place the vials on a flat surface.	
3	Open the Mix2Vial device package by completely peeling away the lid, without touching the inside of the package. Do not remove the Mix2Vial device from the package.	NA

4	<p>Turn the package with the Mix2Vial device upside down and place it over the top of the solvent vial. Firmly insert the blue plastic spike of the device into the centre of the solvent vial stopper by pushing straight down. Grip the package at its edge and lift it off the Mix2Vial device. Be careful not to touch the clear plastic spike. The solvent vial now has the Mix2Vial device connected to it and is ready to be connected to the VEYVONDI vial.</p>	
5	<p>To connect the solvent vial to the VEYVONDI vial, turn the solvent vial over and place it on top of the vial containing VEYVONDI powder. Fully insert the clear plastic spike into the VEYVONDI vial stopper by firmly pushing straight down. This should be done right away to keep the liquid free of germs. The solvent will flow into the VEYVONDI vial by vacuum. Check that all the solvent has transferred. Do not use if the vacuum has been lost and the solvent does not flow into the VEYVONDI vial.</p>	
6	<p>Gently and continuously swirl the connected vials or allow the reconstituted product to stand for 5 minutes then gently swirl to ensure the powder is completely dissolved. Do not shake. Shaking will adversely affect the product. Do not refrigerate after reconstitution.</p>	
7	<p>Disconnect the two sides of the Mix2Vial from each other by holding the clear plastic side of the Mix2Vial device attached to the VEYVONDI vial with one hand and the blue plastic side of the Mix2Vial device attached to the solvent vial with the other hand. Turn the blue plastic side counterclockwise and gently pull the two vials apart. Do not touch the end of the plastic connector attached to the VEYVONDI vial containing the dissolved product. Place the VEYVONDI vial on a flat work surface. Discard the empty solvent vial.</p>	
8	<p>Draw air into the empty, sterile disposable plastic syringe by pulling back on the plunger. The amount of air should equal the amount of reconstituted VEYVONDI that you will withdraw from the vial.</p>	
9	<p>Leaving the VEYVONDI vial (containing the reconstituted product) on your flat work surface, connect the syringe to the clear plastic connector and turning the syringe clockwise.</p>	

10	Hold the vial with one hand and use the other hand to push all the air from the syringe into the vial.	
11	Flip connected syringe and VEYVONDI vial so the vial is on top. Be sure to keep the syringe plunger pressed in. Draw the VEYVONDI into the syringe by pulling plunger back slowly.	
12	Do not push and pull solution back and forth between syringe and vial. Doing so may harm medicine. When ready to infuse, disconnect the syringe by turning it counterclockwise. Inspect the syringe visually for particulate matter; the solution should be clear and colourless. If flakes or particles are seen, do not use the solution and notify your doctor.	
13	<p>If you need more than one vial of VEYVONDI to make up your dose:</p> <ul style="list-style-type: none"> • Leave the syringe attached to the vial until an additional vial is prepared. • Use the reconstitution steps above (2 to 8) to prepare the additional vial of VEYVONDI using a fresh Mix2Vial device for each vial. 	
14	The contents of two vials may be drawn into a single syringe. NOTE: When pushing air into a second vial of VEYVONDI to be pooled into a syringe, orient the vial and connected syringe with the vial on top.	

Instructions for Administration

Inspect the prepared solution in the syringe for particulate matter and discoloration prior to administration (the solution should be clear, colourless and free from particles). It is not uncommon for a few flakes or particles to remain in the **product vial after reconstitution**. The filter included in the Mix2Vial device removes those particles completely. Filtration does not influence dosage calculations. **The solution in the syringe** should not be used if it is cloudy or contains flakes or particles after filtration.

1. Attach the infusion needle to a syringe containing VEYVONDI solution. For comfort, a winged (butterfly) infusion set is preferred. Point the needle up and remove any air bubbles by gently tapping the syringe with your finger and slowly and carefully pushing air out of the syringe and needle.

2. Apply a tourniquet and get the infusion site ready by wiping the skin well with a sterile alcohol swab (or other suitable sterile solution suggested by your doctor or haemophilia treatment centre).
3. Insert the needle into the vein and remove the tourniquet. Slowly infuse VEYVONDI. Do not infuse any faster than 4 mL per minute. Disconnect the empty syringe. If your dose requires multiple syringes, attach and administer each additional syringe of VEYVONDI one at a time.

Note:

Do not remove butterfly needle until all syringes have been infused and do not touch the Luer port that connects to the syringe.

If recombinant factor VIII has been prescribed, administer recombinant factor VIII within 10 minutes after infusion of VEYVONDI has been completed.

4. Take the needle out of the vein and use sterile gauze to put pressure on the infusion site for several minutes.

In case large volumes of VEYVONDI are required, it is possible to pool two vials of VEYVONDI together. The contents of each reconstituted product of VEYVONDI can be drawn in a single syringe. However, in these cases the initially reconstituted solution of VEYVONDI should not be diluted any further.

The solution should be slowly administered intravenously (see section 4.2) not exceeding 4 mL/min. Do not recap the needle. Place the needle, syringe, and empty VEYVONDI and solvent vial(s) in a hard-walled sharps container for proper disposal. Do not dispose of these supplies in ordinary household trash.

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

7. MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH
Industriestraße 67
1221 Vienna
Austria

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1298/001
EU/1/18/1298/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31 August 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) 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 SUBSTANCE AND
MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturers of the biological active substance

Baxalta Manufacturing Sàrl
Route de Pierre-à -Bot 111
2000 Neuchâtel
SWITZERLAND

Name and address of the manufacturers responsible for batch release

Takeda Manufacturing Austria AG
Industriestrasse 67
1221 Vienna
AUSTRIA

Baxter AG
Industriestrasse 67
1221 Vienna
AUSTRIA

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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).

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING
AUTHORISATION**

• **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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 marketing authorisation holder (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.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (650 IU)

1. NAME OF THE MEDICINAL PRODUCT

VEYVONDI 650 IU powder and solvent for solution for injection
vonico α (recombinant human von Willebrand factor)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 650 IU vonico α , approx. 130 IU/mL after reconstitution with 5 mL water for
Injections
Specific activity: approx. 110 IU VWF:RC α /mg protein

3. LIST OF EXCIPIENTS

Excipients: Sodium citrate, glycine, trehalose dihydrate, mannitol, polysorbate 80, and water for
injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents: 1 powder vial, 1 vial with solvent (5 mL), 1 Mix2Vial device

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use, after reconstitution.
Single use only.
Read the package leaflet before 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:

Use immediately or within 3 hours after reconstitution.

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.
Do not freeze.
Store in the original package 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

Baxalta Innovations GmbH
Industriestraße 67
1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1298/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

VEYVONDI 650 IU

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (1300 IU)

1. NAME OF THE MEDICINAL PRODUCT

VEYVONDI 1300 IU powder and solvent for solution for injection
vonico α (recombinant human von Willebrand factor)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 1300 IU vonico α , approx. 130 IU/mL after reconstitution with 10 mL Water for Injections
Specific activity: approx. 110 IU VWF:RC α /mg protein

3. LIST OF EXCIPIENTS

Excipients: Sodium citrate, glycine, trehalose dihydrate, mannitol, polysorbate 80 and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents: 1 powder vial, 1 vial with solvent (10ml), 1 Mix2Vial device

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use, after reconstitution.
Single use only.
Read the package leaflet before 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:

Use immediately or within 3 hours after reconstitution.

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.
Do not freeze.
Store in the original package 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

Baxalta Innovations GmbH
Industriestraße 67
1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1298/002

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

VEYVONDI 1300 IU

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

POWDER VIAL LABEL

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

VEYVONDI 650 IU powder
vonicog alfa
IV

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
Single use only.

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
POWDER VIAL LABEL

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

VEYVONDI 1300 IU powder
vonicog alfa
IV

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
Single use only.

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SOLVENT VIAL LABEL (5mL)

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

Solvent for VEYVONDI
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

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
SOLVENT VIAL LABEL (10 mL)

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

Solvent for VEYVONDI
Water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

VEYVONDI 650 IU powder and solvent for solution for injection **VEYVONDI 1300 IU powder and solvent for solution for injection** vonicoq alfa

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

What is in this leaflet

1. What VEYVONDI is and what it is used for
2. What you need to know before you use VEYVONDI
3. How to use VEYVONDI
4. Possible side effects
5. How to store VEYVONDI
6. Contents of the pack and other information

1. What VEYVONDI is and what it is used for

VEYVONDI contains the active substance vonicoq alfa, which is a recombinant human von Willebrand factor (rVWF). It behaves in the same way as natural human von Willebrand factor (VWF) in the body. VWF is the carrier molecule for coagulation factor VIII and is involved in blood clotting making platelets stick to wounds and so helps to form a blood clot. Lack of VWF increases the tendency to bleed.

VEYVONDI is used to treat and control bleeding episodes and to prevent bleeding during surgery in adult patients (aged 18 years and older) with von Willebrand disease. It is used when treatment with another medicine, desmopressin, is not effective or cannot be given.

Von Willebrand disease is an inherited bleeding disorder caused by the lack or an insufficient amount of von Willebrand factor. In patients with the disease the blood does not clot normally leading to a prolonged bleeding time. Administration of von Willebrand factor (VWF) allows for correction of von Willebrand factor deficiency.

2. What you need to know before you use VEYVONDI

Do not use VEYVONDI

- if you are allergic to vonicoq alfa or any of the other ingredients of this medicine (listed in section 6)
- if you are allergic to mouse or hamster proteins

If you are unsure about this, ask your doctor.

Warnings and precautions

Talk to your doctor before using VEYVONDI

There is a risk that you may experience a hypersensitivity reaction (a severe, sudden allergic reaction) to VEYVONDI. Your doctor should inform you about early signs of severe allergic reactions such as increased heart rate, rash, hives, wheals, generalised itching, swelling of lips and tongue, difficulty in breathing, wheezing, tightness in the chest, fast heartbeat, stuffy nose, red eyes, general feeling of being unwell, and dizziness. These could be early symptoms of a hypersensitivity reaction. **If any of these symptoms occur, stop the infusion immediately and contact your doctor. Severe symptoms, including difficulty in breathing and dizziness, require prompt emergency treatment.**

Patients developing inhibitors

Inhibitors (antibodies) against the VWF may occur in some patients receiving the medicine. These inhibitors, especially at high levels, could cause the treatment to stop working properly. You will be monitored carefully for the possibility of having developed these inhibitors.

- If your bleeding is not controlled with VEYVONDI, tell your doctor immediately.

If your plasma VWF or factor VIII fail to reach the expected levels with VEYVONDI based on the test results followed by your doctor, or if bleeding is not adequately controlled, it could be due to the presence of VWF or factor VIII antibodies. This will be checked by your doctor. You might need a higher dose of VEYVONDI, or a higher dose of factor VIII, or even a different medicine to control bleedings. Do not increase the total dose of VEYVONDI to control your bleeding without consulting your doctor.

If you have previously been treated with plasma-derived VWF concentrates you may have reduced response to VEYVONDI due to pre-existing antibodies. Your doctor may adjust the dose according to your laboratory results.

Thrombolism and embolism

There is a risk of occurrence of thrombotic events if you have known clinical or laboratory risk factors. Therefore your doctor will monitor you for early signs of thrombosis.

FVIII products may contain varying amounts of VWF. Therefore, any FVIII product that would be administered in combination with VEYVONDI should be a pure FVIII product.

If you previously had problems with blood clots or vessel occlusion (thromboembolic complications), tell your doctor immediately.

Children and adolescents

VEYVONDI is not approved for use in children or adolescents below 18 years.

Other medicines and VEYVONDI

Tell your doctor if you are using, have recently used or might use 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 for advice before taking this medicine.

Driving and using machines

VEYVONDI is not likely to affect your ability to drive and use machines.

VEYVONDI contains sodium

This medicine contains 5.2 mg sodium in each 650 IU vial or 10.4 mg sodium in each 1300 IU vial. This is equivalent to 2.2% of the recommended maximum daily dietary intake of sodium for an adult, assuming 70 kg body weight and 80 IU/kg body weight.

This should be taken into consideration if you are on a controlled sodium diet.

3. How to use VEYVONDI

Your treatment with VEYVONDI will be supervised by a doctor who is experienced in the care of patients with von Willebrand disease.

Your doctor will calculate your dose of VEYVONDI (in international units or IU). The dose depends on:

- body weight,
- the site of the bleeding
- intensity of the bleeding,
- your clinical condition,
- the required surgery
- the VWF activity levels in your blood after surgery
- the severity of your disease

Your doctor may test your blood to make sure that you have adequate levels of von Willebrand factor. This is particularly important if you are having major surgery.

Treatment of bleeding episodes

Your doctor will calculate the dose that is most appropriate for you, how often you should receive VEYVONDI and for how long.

For minor bleeding (e.g. nose bleed, oral bleeding, menorrhagia), each initial dose is usually 40 to 50 IU/kg and for major bleeding (severe or refractory nose bleed, menorrhagia, gastrointestinal bleeding, Central nervous system trauma, haemarthrosis, or traumatic haemorrhage), each initial dose is 50 to 80 IU/kg. Subsequent doses (as clinically required) are 40 to 50 IU/kg every 8 to 24 hours for minor bleeds as long as deemed clinically necessary and for major bleeds 40 to 60 IU/kg for approximately 2-3 days.

If you feel that VEYVONDI is not working well enough, talk to your doctor. Your doctor will perform tests to make sure that you have adequate levels of von Willebrand factor. If you use VEYVONDI at home, your doctor will make sure that you are shown how to infuse it and how much to use.

Prevention of bleeding in case of elective surgery

For prevention of excessive bleeding your doctor will assess the FVIII:C levels within 3 hours before surgery. If your FVIII level is inadequate your doctor may give you a dose of 40-60 IU/kg VEYVONDI 12-24 hours (pre-operative dose) prior to initiating elective surgery in order to raise FVIII levels to the target level (0.4 IU/mL for minor and at least 0.8 IU/mL for major surgery). Within 1 hour prior to surgery, you will receive a dose of VEYVONDI based on the assessment 3 hours before surgery. The dose depends on VWF and FVIII levels of the patient, the type and severity of the expected bleeding.

How VEYVONDI is given

VEYVONDI is usually infused into a vein (intravenously) by your doctor or nurse. Detailed instructions for reconstitution and administration are given at the end of this package leaflet.

Use in children and adolescents

VEYVONDI is not approved for use in children and adolescents below 18 years.

If you use more VEYVONDI than you should

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. If you infuse more VEYVONDI than recommended, tell your doctor as soon as possible. There may be a risk of developing blood clots (thrombosis) in case of an accidental high dose.

If you forget to use VEYVONDI

- Do not infuse a double dose to make up for a forgotten dose.
- Proceed with the next infusion as scheduled and continue as advised by your doctor.

If you stop using VEYVONDI

Do not stop using VEYVONDI without consulting your doctor.

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

4. Possible side effects

Like all medicines, this medicine may cause side effects, although not everybody gets them.

You can have a serious allergic reaction to VEYVONDI.

You must **stop the infusion** and **contact your doctor immediately** if you have any of the following early symptoms of severe allergic reactions:

- rash or hives, itching all over the body,
- tightness of the throat, chest pain or chest tightness,
- difficulty breathing, light headedness, fast heartbeat,
- dizziness, nausea or fainting.

Side effects that have been reported with VEYVONDI that can occur commonly (up to 1 in 10 patients) are: nausea, vomiting, tingling or burning at infusion site, chest discomfort, dizziness, vertigo, blood clots, hot flushes, itching, high blood pressure, muscle twitching, unusual taste, and increased heart rate.

Reporting of side effects

If you get any side effects, talk to your doctor. 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 VEYVONDI

- 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 after EXP. The expiry date refers to the last day of that month.
- Do not store above 30°C.
- Do not freeze.
- Keep the vial in the outer carton in order to protect from light.
- Do not refrigerate the solution after preparation.

- Use the reconstituted product within 3 hours to avoid the risk of microbial contamination because the product does not contain preservatives.
- This medicine is for single use only. Discard any unused solution appropriately.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What VEYVONDI contains

The active substance is vonicog alfa (recombinant human von Willebrand factor).

VEYVONDI 650 IU powder and solvent for solution for injection

Each vial of powder contains nominally 650 International Units (IU) vonicog alfa.

After reconstitution with the 5 mL solvent provided, VEYVONDI contains approximately 130 IU/mL vonicog alfa.

VEYVONDI 1300 IU powder and solvent for solution for injection

Each vial of powder contains nominally 1300 International Units (IU) vonicog alfa.

After reconstitution with the 10 mL solvent provided, VEYVONDI contains approximately 130 IU/mL vonicog alfa.

The other ingredients are:

- Sodium citrate, glycine, trehalose dihydrate, mannitol, polysorbate 80 and water for injections.
- See section 2 “VEYVONDI contains sodium”.

What VEYVONDI looks like and contents of the pack

VEYVONDI is a white to off-white powder. After reconstitution, when drawn into the syringe, the solution is clear, colourless in appearance and free from flakes or other foreign particles.

Each pack of VEYVONDI 650 IU contains:

- powder in a glass vial with a rubber stopper
- 5 mL of solvent in a glass vial with a rubber stopper
- one reconstitution device (Mix2Vial)

Each pack of VEYVONDI 1300 IU contains:

- powder in a vial (type I glass), with a butyl rubber stopper
- 10 mL of solvent in a vial (type I glass), with a rubber stopper (bromobutyl)
- one reconstitution device (Mix2Vial)

Marketing Authorisation Holder

Baxalta Innovations GmbH
 Industriestraße 67
 1221 Vienna
 Austria
 Tel: +44(0)1256 894 959
 e-mail: medinfoEMEA@shire.com

Manufacturer

Takeda Manufacturing Austria AG
Industriestrasse 67
1221 Vienna
Austria

Baxter AG
Industriestraße 67
1221 Vienna
Austria

This leaflet was last revised in .

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

Instructions for preparation and administration

General instructions

Check the expiry date, and ensure that the VEYVONDI powder and water for injections (solvent) are at room temperature prior to preparation. Do not use after the expiry date stated on the labels and carton.

Use antiseptic technique (clean and low-germ conditions) and a flat work surface during the reconstitution procedure. Wash your hands and put on clean exam gloves (the use of gloves is optional).

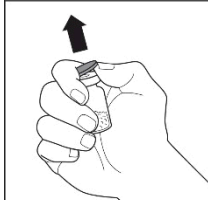
Use the reconstituted product (after mixing the powder with the supplied water) as soon as possible and within three hours. You can store the reconstituted product at room temperature not to exceed 25°C for up to three hours. Reconstituted product should not be refrigerated. Discard after three hours.


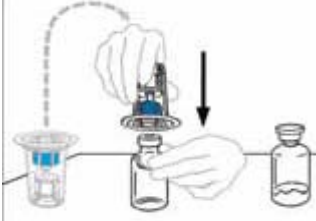
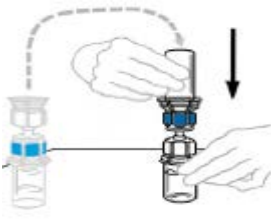
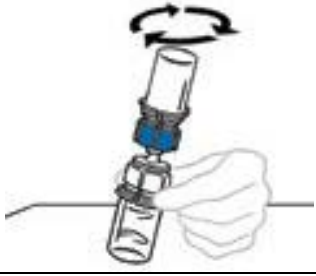

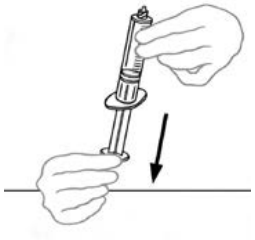
Ensure that the VEYVONDI powder vial and the Sterilised Water for Injections (solvent) are at room temperature prior to preparation.


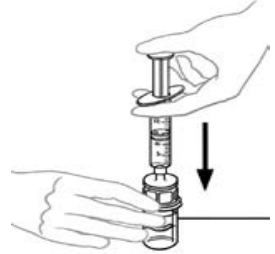
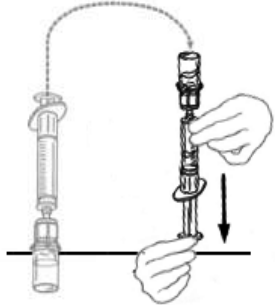

Use plastic syringes with this product because proteins in the product tend to stick to the surface of glass syringes.

Do not mix VEYVONDI with other medicinal products except for rFVIII.

Instructions for reconstitution

	Steps	Image example
1	Remove the caps from the VEYVONDI powder and solvent vials to expose the centre of the rubber stoppers.	

2	Disinfect each stopper with a separate sterile alcohol swab (or other suitable sterile solution suggested by your doctor or haemophilia treatment centre) by wiping the stopper for several seconds. Allow the rubber stoppers to dry. Place the vials on a flat surface.	
3	Open the Mix2Vial device package by completely peeling away the lid, without touching the inside of the package. Do not remove the Mix2Vial device from the package.	NA
4	Turn the package with the Mix2Vial device upside down and place it over the top of the solvent vial. Firmly insert the blue plastic spike of the device into the centre of the solvent vial stopper by pushing straight down. Grip the package at its edge and lift it off the Mix2Vial device. Be careful not to touch the clear plastic spike. The solvent vial now has the Mix2Vial device connected to it and is ready to be connected to the VEYVONDI vial.	
5	To connect the solvent vial to the VEYVONDI vial, turn the solvent vial over and place it on top of the vial containing VEYVONDI concentrate. Fully insert the clear plastic spike into the VEYVONDI vial stopper by firmly pushing straight down. This should be done right away to keep the liquid free of germs. The solvent will flow into the VEYVONDI vial by vacuum. Check that all the solvent has transferred. Do not use if vacuum has been lost and the solvent does not flow into the VEYVONDI vial.	
6	Gently and continuously swirl the connected vials or allow the reconstituted product to stand for 5 minutes then gently swirl to ensure the powder is completely dissolved. Do not shake. Shaking will adversely affect the product. Do not refrigerate after reconstitution.	
7	Disconnect the two sides of the Mix2Vial from each other by holding the clear plastic side of the Mix2Vial device attached to the VEYVONDI vial with one hand and the blue plastic side of the Mix2Vial device attached to the solvent vial with the other hand. Turn the blue plastic side counterclockwise and gently pull the two vials apart. Do not touch the end of the plastic connector attached to the VEYVONDI vial containing the dissolved product. Place the VEYVONDI vial on a flat work surface. Discard the empty solvent vial.	
8	Draw air into the empty, sterile disposable plastic syringe by pulling back on the plunger. The amount of air should equal the amount of reconstituted VEYVONDI that you will withdraw from the vial.	

9	Leaving the VEYVONDI vial (containing the dissolved product) on your flat work surface, connect the syringe to the clear plastic connector by attaching and turning the syringe clockwise.	
10	Hold the vial with one hand and use the other hand to push all the air from the syringe into the vial	
11	Flip connected syringe and VEYVONDI vial so the vial is on top. Be sure to keep the syringe plunger pressed in. Draw the VEYVONDI into the syringe by pulling plunger back slowly.	
12	Do not push and pull solution back and forth between syringe and vial. Doing so may harm the medicine. When ready to infuse, disconnect the syringe by turning it counterclockwise. Inspect the syringe visually for particulate matter; the solution in the syringe should be clear. If flakes or particles are seen, do not use the solution and notify your doctor.	
13	If you need more than one vial of VEYVONDI to make up your dose: <ul style="list-style-type: none"> • Leave the syringe attached to the vial until an additional vial is prepared. • Use the reconstitution steps above (2 to 8) to prepare the additional vial of VEYVONDI using a fresh Mix2Vial for each vial 	
14	The contents of two vials may be drawn into a single syringe. NOTE: When pushing air into a second vial of VEYVONDI to be pooled into a syringe, position the vial and connected syringe so that the vial is on top.	

Instructions for administration

Inspect the prepared solution in the syringe for particulate matter and discoloration prior to administration (the solution should be clear, colourless and free from particles). It is not uncommon for a few flakes or particles to remain in the **product vial after reconstitution**. The filter included in the Mix2Vial device removes those particles completely. Filtration does not influence dosage

calculations. **The solution in the syringe** should not be used if it is cloudy or contains flakes or particles after filtration.

1. Attach the infusion needle to a syringe containing VEYVONDI solution. For comfort, a winged (butterfly) infusion set is preferred. Point the needle up and remove any air bubbles by gently tapping the syringe with your finger and slowly and carefully pushing air out of the syringe and needle.
2. Apply a tourniquet and get the infusion site ready by wiping the skin well with a sterile alcohol swab (or other suitable sterile solution suggested by your doctor or haemophilia treatment centre).
3. Insert the needle into the vein and remove the tourniquet. Slowly infuse VEYVONDI. Do not infuse any faster than 4 mL per minute. Disconnect the empty syringe. If your dose requires multiple syringes, attach and administer each additional syringe of VEYVONDI one at a time.

Note:

Do not remove butterfly needle until all syringes have been infused and do not touch the Luer port that connects to the syringe.

If recombinant factor VIII has been prescribed, administer recombinant factor VIII within 10 minutes after infusion of VEYVONDI has been completed.

4. Take the needle out of the vein and use sterile gauze to put pressure on the infusion site for several minutes.

In case large volumes of VEYVONDI are required, it is possible to pool two vials of VEYVONDI together. The contents of each reconstituted product of VEYVONDI can be drawn in a single syringe. However, in these cases the initially reconstituted solution should not be diluted any further.

Do not recap the needle. Place the needle, syringe, and empty VEYVONDI and solvent vial(s) in a hard-walled sharps container for proper disposal. Do not dispose of these supplies in ordinary household trash.

The following information is intended for healthcare professionals only:

Treatment of bleeding episodes (On-demand treatment)

Dosage and frequency must be individualized based on clinical judgment, taking into account of severity of bleeding episode, site of bleeding, patient’s medical history, monitoring of appropriate clinical and laboratory measures (both VWF:RCo and FVIII:C levels).

Start of treatment

VEYVONDI should be administered with recombinant factor VIII if the FVIII:C levels are <40%, or are unknown, to control bleeding. The rFVIII dose should be calculated according to the difference between the patient’s baseline plasma FVIII:C level, and the desired peak FVIII:C level to achieve an appropriate plasma FVIII:C level based on the approximate mean recovery of 0.02 (IU/mL)/(IU/kg). The complete dose of VEYVONDI should be administered followed by rFVIII within 10 minutes.

Calculating dose

VEYVONDI dose [IU] = dose [IU/kg] x weight [kg]

Subsequent infusions

Administer a subsequent dose of 40 IU to 60 IU/kg of VEYVONDI infused every 8 to 24 hours as per the dosing ranges in Table 1, as long as clinically required. In major bleeding episodes, maintain trough levels of VWF:RCo greater than 50% for as long as deemed necessary.

Table 1
Dosing recommendations for the treatment of Minor and Major Haemorrhages

Haemorrhage	Initial Dose ^a (IU VWF:RCo/kg body weight)	Subsequent Dose
Minor (e.g. epistaxis, oral bleeding, menorrhagia)	40 to 50 IU/kg	40 to 50 IU/kg every 8 to 24 hours (or as long as deemed clinically necessary)
Major ^b (e.g. severe or refractory epistaxis, menorrhagia, Gastrointestinal bleeding, Central nervous system trauma, haemarthrosis, or traumatic haemorrhage)	50 to 80 IU/kg	40 to 60 IU/kg every 8 to 24 hours for approximately 2-3 days (or as long as deemed clinically necessary)

^aIf rFVIII is administered, see rFVIII package insert for reconstitution and administration instructions.

^bA bleed could be considered major if red blood cell transfusion is either required or potentially indicated or if bleeding occurs in a critical anatomical site (e.g., intracranial or gastrointestinal haemorrhage).

Prevention of bleeding/haemorrhage and treatment in case of elective surgery

Assess FVIII:C levels prior to initiation of any surgical procedure. The recommended minimum target levels are 0.4 IU/mL for minor and oral surgery and 0.8 IU/mL for major surgery.

To ensure pre-operative endogenous FVIII levels of at least 0.4 IU/mL for minor and oral and 0.8 IU/mL for major surgery, a dose of 40-60 IU/kg VEYVONDI may be administered 12-24 hours (pre-operative dose) prior to initiating elective surgery. Within 1 hour prior to surgery, patients should

receive a dose of VEYVONDI based on the assessment 3 hours before surgery. The dose depends on VWF and FVIII levels of the patient, the type and severity of the bleeding.

If the FVIII:C levels are not at the recommended target, a dose of VEYVONDI alone should be administered within 1 hour prior to the procedure. If the FVIII:C levels are not at the recommended target levels, rFVIII should be administered in addition to vonicog alfa to raise VWF:RCo and FVIII:C. Please refer to (Table 2) for FVIII:C recommended target levels.

Table 2
VWF:RCo and FVIII:C Target Levels
Recommended Target Peak Plasma Levels of VWF:RCo and FVIII:C to be Achieved Prior to Surgery for the Prevention of Excessive Bleeding During and After Surgery

Type of Surgery	VWF:RCo Target Peak Plasma Level	FVIII:C Target Peak Plasma Level ^a	Calculation of rVWF dose (to be administered within 1 hour prior to surgery) (IU VWF:RCo required)
Minor	0.5-0.6 IU/mL	0.4 – 0.5 IU/mL	$\Delta^b \text{VWF:RCo} \times \text{BW (kg)} / \text{IR}^c$
Major	1 IU/mL	0.80 - 1 IU/mL	$\Delta^b \text{VWF:RCo} \times \text{BW (kg)} / \text{IR}^c$

^a Additional rFVIII may be required to attain the recommended FVIII:C target peak plasma levels. Dosing guidance should be done based on the IR.

^b Δ = Target peak plasma VWF:RCo – baseline plasma VWF:RCo

^c IR = Incremental Recovery as measured in the subject. If the IR is not available, assume an IR of 0.02 IU/mL per IU/kg.

During and After Surgery

After the initiation of the surgical procedure, the VWF:RCo and FVIII:C plasma levels should be monitored and the intra- and post-operative substitution regimen should be individualized according to the PK results, intensity and duration of the haemostatic challenge, and the institution's standard of care. In general, the frequency of VEYVONDI dosing for post-operative substitution should range from twice a day to every 48 hours. Refer to Table 3 for treatment recommendations for subsequent maintenance doses.

Table 3
Recommended Target Trough Plasma Levels of VWF:RCo and FVIII:C and Minimum Duration of Treatment for Subsequent Maintenance Doses for the Prevention of Excessive Bleeding After Surgery

Type of Surgery	VWF:RCo Target Trough Plasma Level		FVIII:C Target Trough Plasma Level		Minimum Duration of treatment	Frequency of dosing
	Up to 72 hours post surgery	After 72 hours post surgery	Up to 72 hours post surgery	After 72 hours post surgery		
Minor	≥ 0.30 IU/mL	-	> 0.40 IU/mL	-	48 hours	Every 12-24 hrs / every other day
Major	> 0.50 IU/mL	> 0.30 IU/mL	> 0.50 IU/mL	> 0.40 IU/mL	72 hours	Every 12-24 hrs / every other day

Name and batch number of the medicinal product

It is strongly recommended that every time that VEYVONDI 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.