SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

VEYVONDI 650 IU powder and solvent for solution for injection
VEYVONDI 1 300 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 1 300 IU powder and solvent for solution for injection

Each vial of powder contains nominally 1 300 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 Pharmacopeia 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).

Excipients with known effect

Each 650 IU powder vial contains 5.2 mg sodium and 0.5 mg of polysorbate 80.

Each 1 300 IU powder vial contains 10.4 mg sodium and 1.0 mg of polysorbate 80.

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

Prevention and treatment of haemorrhage or surgical bleeding in adults (aged 18 years and older) with von Willebrand disease (VWD), when desmopressin (DDAVP) treatment alone is ineffective or contraindicated.

Treatment of haemorrhage in children (aged less than 18 years) with von Willebrand disease (VWD), when desmopressin (DDAVP) treatment alone is ineffective or contraindicated.

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

Dose 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 (≥ 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) in adults and children

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
VEYVONDI dose [IU] = dose [IU/kg] x body 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 trials, 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)

[a] If rFVIII is administered, see rFVIII package insert for reconstitution and administration instructions.
[b] A 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 in adults

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 pharmacokinetics (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

Prophylactic treatment in adults

For initiation of long-term prophylaxis against bleeds in patients with VWD, doses of 40 to 60 IU/kg of VEYVONDI administered twice weekly should be considered. Depending on the patient's condition and clinical response, including breakthrough bleeds, higher doses (not exceeding 80 IU/kg) and/or an increased dose frequency (up to three times per week) may be required.

Paediatric population

The safety and efficacy of VEYVONDI in children aged less than 18 years have been established for the treatment of haemorrhage. Dosing is based on the same guidelines as for adults and should be adjusted to the clinical condition of the patient, as well as their VWF:RCo and FVIII:C plasma levels. In younger patients, shorter dose intervals or higher doses may be necessary (see section 5.2). The safety and efficacy of VEYVONDI for prophylactic treatment or the prevention or treatment of surgical bleeding have not yet been established in children aged less than 18 years.

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.

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 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 level for FVIII:C activity should be monitored to avoid sustained excessive FVIII:C plasma level, 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.

Neutralising antibodies (inhibitors)

Patients with VWD, especially type 3, may develop neutralising antibodies (inhibitors) to von Willebrand factor. If the expected plasma level of (VWF:RCo) is 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 neutralising antibodies, von Willebrand factor therapy may not be effective and other therapeutic options should be considered to establish haemostasis.

Treatment of VWD patients who have high-titer binding antibodies [due to previous treatment with plasma derived von Willebrand factor (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

Sodium content

This medicinal product contains 5.2 mg sodium in each 650 IU vial or 10.4 mg sodium in each
1 300 IU vial, 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.

Polysorbate content

This medicinal product contains 0.5 mg of polysorbate 80 in each 650 IU vial or 1.0 mg of polysorbate 80 in each 1 300 IU vial, which is equivalent to 0.1 mg/mL. Polysorbates may cause allergic reactions.

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
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 (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in 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**
Immune system disorders	Anaphylactic reaction*	Not known
Nervous system disorders	Headache	Very common
	Dizziness	Common
	Vertigo	Common
	Dysgeusia	Uncommon
	Tremor	Uncommon
Cardiac disorders	Tachycardia	Uncommon
Vascular disorders	Hypertension	Common
	Deep venous thrombosis	Uncommon
	Hot flush	Uncommon
Gastrointestinal disorders	Vomiting	Common
	Nausea	Common
Skin and subcutaneous tissue disorders	Pruritus generalised	Common
General disorders and administration site conditions	Chest discomfort	Uncommon
	Infusion site paraesthesia	Uncommon
	Infusion-related reaction (including tachycardia, flushing, rash, dyspnoea, blurred vision)*	Not known
Investigations	Electrocardiogram T wave inversion	Uncommon

	Heart rate increased	Uncommon

* Adverse reactions identified during post-marketing surveillance.

Description of selected adverse reactions

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 VWD, 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 neutralising 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 neutralising antibodies against human VWF or neutralising antibodies against human rFVIII was observed. One of the 132 subjects who received VEYVONDI peri-operatively in clinical trials 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.

Paediatric population

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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: antihaemorrhagics blood coagulation factors, 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, the FVIII:C level is expected to rise above 40% within 6 hours and to peak within 24 hours in most 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 5 completed trials in adults and children with VWD (070701, 071001, 071101, 071301 and SHP677-304) and in one ongoing trial in children with VWD (071102). A total of 144 unique subjects (103 unique adult subjects with VWD, 29 unique paediactric subjects with VWD, 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 one or more 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 trials in adults 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 5 summarizes the PK of VEYVONDI in adults after 50 IU/kg VWR:RCo (PK_{50}) or 80 IU/kg VWF:RCo (PK_{80}) infusions. The mean duration of infusion was 16.5 minutes (SD ± 3.51 minutes) for 50 IU/kg (PK_{50}) and 11.8 minutes (± 2.86 minutes) for 80 IU/kg VWF:RCo (PK_{80}).

Table 5. Pharmacokinetic assessment of VWF:RCo[fa] in adults

Parameter	**Phase 1 PK_{50} VEYVONDI with octocog alfa[g] (Study 070701)** **Mean (95% CI)** **SD**	**Phase 3 PK_{50} VEYVONDI (Study 071001)** **Mean (95% CI)** **SD**	**Phase 3 PK_{80} VEYVONDI (Study 071001)** **Mean (95% CI)** **SD**	**Surgery PK_{50} VEYVONDI (Study 071101)** **Mean (95% CI)** **SD**
$T_{1/2}$[b]	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[c]	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}[d]	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
$AUC_{0\text{-}inf}$[e]	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
$AUC_{0\text{-}inf}$/Dose[f]	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] [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.
[b] [hours]
[c] [dL/kg/hours]
[d] [(IU/dL)/(IU VWF:RCo/kg)]
[e] [(h*IU/dL)]
[f] [(h*IU/dL)/(IU VWF:RCo/kg)]
[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 $AUC_{0\text{-}inf}$ 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 plasma derived factor VIII (pdFVIII) (50 IU/kg pdVWF:RCo and 38.5 IU/kg pdFVIII).

In addition, full PK assessments of VEYVONDI were performed following single and multiple dosing in study 071301, which investigated long-term prophylactic treatment in a total of 23 adult subjects with severe VWD (N=3 type 1, N=1 type 2A, N=1 type 2B, N=18 type 3). PK parameters derived from these assessment confirmed the results of previous trials (see Table 5 above) and a statistical comparison of key VWF PK parameters between initiation and month 12 of prophylactic treatment did not reveal any significant differences.

PK data of VWF (N=134) across the 6studies were evaluated using a population PK modelling and simulation approach. These results confirmed that the PK of VWF:RCo is both dose-independent (range: 2.0 to 80 IU/kg) and time-independent (up to 4.3 years). Covariate evaluations indicated no clinically meaningful effect of gender, race or VWD type on VWF:RCo PK; body weight and age were identified as significant covariates.

Paediatric population

PK of VWF in 24 paediatric patients with VWD were estimated based on population PK modelling using sparse PK samples collected during a paediatric study across three age groups (less than 6 years old [N=5], 6 years to less than 12 years old [N=10], and 12 years to less than 18 years old [N=9]) after receiving a single infusion of 50 ± 5 IU/kg rVWF:RCo (see Table 6).

Table 6. Pharmacokinetic assessment of VWF:RCo in paediatric subjects[a]

Parameter	PK50 VEYVONDI (Study 071102) Mean (95% CI) SD			
Age range	**< 6 yrs (n=5)**	**6 yrs to < 12 yrs (n=10)**	**12 yrs to < 18 yrs (n=9)**	**Total (n=24)**
$T_{1/2}$[b]	12.4 (9.91; 15.0) 2.90	14.5 (13.6; 15.4) 1.47	15.1 (14.2; 16.1) 1.50	14.3 (13.5; 15.1) 2.03
CL[c]	0.082 (0.047; 0.118) 0.041	0.051 (0.041; 0.061) 0.016	0.043 (0.038; 0.048) 0.007	0.055 (0.045; 0.065) 0.025
IR at C_{max}[d]	1.25 (0.92; 1.58) 0.378	1.54 (1.30; 1.77) 0.378	1.58 (1.43; 1.72) 0.225	1.49 (1.36; 1.63) 0.339
AUC_{0-inf}[e]	1260 (690; 1840)	1630 (1080; 2170)	1600 (1140; 2060)	1540 (1240; 1840)
AUC_{0-inf}/Dose[f]	25.6 (14.4; 36.9) 12.8	32.5 (21.3; 43.7) 18.1	32.6 (23.2; 41.9) 14.3	31.1 (25.0; 37.2) 15.3

[a] Data represent 4 sparse PK samples collected in each subject during paediatric study 071102 and population PK modeling results
[b] [hours]
[c] [dL/kg/hours]
[d] [(IU/dL)/(IU VWF:RCo/kg)]
[e] [(h*IU/dL)]
[f] [(h*IU/dL)/(IU VWF:RCo/kg)]

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 (E 331)
Glycine (E 640)
Trehalose dihydrate
Mannitol (E 421)

Polysorbate 80 (E 433)

Solvent

Water for injections

6.2 Incompatibilities

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.

6.4 Special precautions for storage

Powder

Store below 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 or bromobutyl)
- one reconstitution device (Mix2Vial)

VEYVONDI 1 300 IU powder and solvent for solution for injection

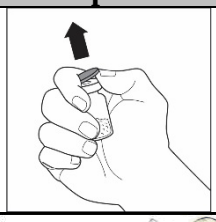
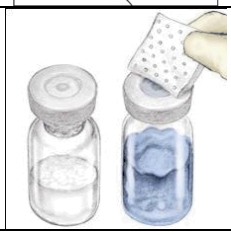
Each pack contains:
- powder in a vial (type I glass), with a butyl rubber stopper
- 10 mL of solvent in a vial (type I glass), with a rubber stopper (bromobutyl)
- one reconstitution device (Mix2Vial)

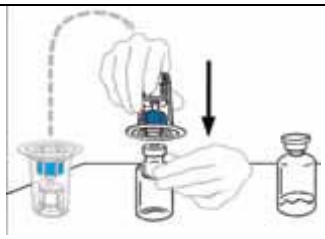
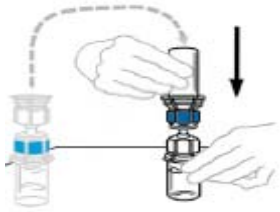
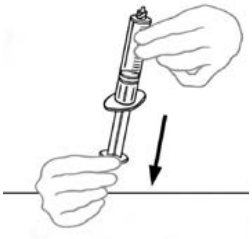
6.6 Special precautions for disposal

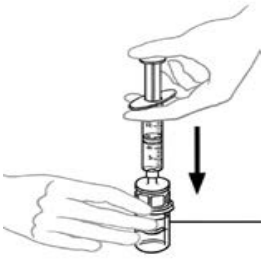
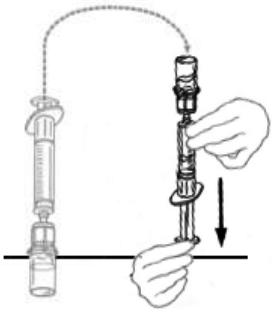
General instructions

- 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 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 octocog alfa (ADVATE).

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	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 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.	
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 reconstituted product) on your flat work surface, connect the syringe to the clear plastic connector and turn 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 should be clear and colourless. 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: • 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, 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 discolouration 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 dose 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

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25/03/2026