AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

Evidence Status Report: Vonicog alfa (Veyvondi®▼) for the on-demand treatment of non-surgical and surgical (elective and emergency) bleeding episodes in children aged up to 17 years with severe von Willebrand disease **(OW19)**

Report prepared by the All Wales Therapeutics and Toxicology Centre
September 2022

KEY FINDINGS

Licence status
Vonicog alfa (VeyvondI®▼) is not licenced for the on-demand treatment of non-surgical and surgical (elective and emergency) bleeding episodes in children aged up to 17 years with severe von Willebrand disease; its use in this indication is off label.

Clinical evidence:
The evidence of clinical efficacy of vonicog alfa in this setting comes mainly from two clinical trials in the adult population. Both trials concluded vonicog alfa is safe and haemostatically effective in adults with severe von Willebrand disease in a variety of clinical bleeding presentations. Data in children are lacking.

Safety
Safety data in children are lacking. Most of the treatment-related adverse events reported in the adult studies were mild to moderate in severity.

Patient factors
Vonicog alfa is licensed in adults and routinely commissioned by the Welsh Health Specialised Services Committee (WHSSC) for treatment of haemorrhage and surgical bleeding, and prevention of surgical bleeding, in adults (aged 18 years or older) with a confirmed diagnosis of VWD, in the following circumstances:

- when desmopressin with or without tranexamic acid treatment is ineffective or not indicated (based on UK clinical practice)
- when von Willebrand factor (VWF) activity levels are <50 IU/dl OR diagnosis is type 2N VWD
- there is no evidence of inhibitors to VWF

It is expected that vonicog alfa will be used in the same circumstances as above for paediatric patients if licenced.

Cost effectiveness
No studies on the cost effectiveness of vonicog alfa were identified for the adult or paediatric populations.

Budget impact
The addition of vonicog alfa as second line treatment is estimated to increase the spend associated with this patient group in Wales by [commercial in confidence text removed] per year between 2022 and 2024.

Impact on health and social care services
Minimal increased use of existing services.

Innovation and/or advantages
Welsh clinical experts indicate an unmet need in this population. Currently second line treatment is derived from human plasma and includes von Willebrand factor in combination with factor VIII. While plasma products used in the UK have an excellent recent safety history, there remains a theoretical risk of plasma-borne pathogen transmission.

Background

Clinicians in Wales consider there is an unmet need and have identified a cohort of patients who could benefit from this treatment. All Wales Therapeutics and Toxicology Centre (AWTTC)-sought clinical expert opinion state children with von Willebrand's disease are currently treated with a licensed product such as Voncento®. This is plasma-derived made from pooling large numbers of blood donations from multiple donors and a theoretical risk of exposure to plasma-borne pathogens exists.

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[1].

Vonicog alfa is routinely commissioned by WHSSC for the licensed treatment of haemorrhage and surgical bleeding, and prevention of surgical bleeding, in adults (aged 18 years or older). If licensed for use in children, WHSSC have confirmed they will consider extending commissioning to include the paediatric population.

Target Group

The indication under consideration is for the on-demand treatment of non-surgical and surgical (elective and emergency) bleeding episodes in children aged up to 17 years with severe von Willebrand disease.

Marketing authorisation date: Not applicable, off-label

Vonicog alfa (Veyvondi®▼) is not licenced in children aged up to 17 years with severe von Willebrand disease (VWD) for on-demand treatment of non-surgical and surgical (elective and emergency) bleeding; its use in this indication is off label.

Vonicog alfa (Veyvondi®▼) is licenced in adults (age 18 and older) with VWD, when desmopressin (DDAVP) treatment alone is ineffective or not indicated for the:

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

Dosing information

Dosage and frequency of administration must be individualised 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[1]. Dosing may require adjustment in underweight or overweight patients. Further information about dose calculations can be found in the Summary of Product Characteristics (SPC)[1].

Clinical Background

VWD is an inherited genetic disorder caused by a missing or defective clotting glycoprotein called von Willebrand factor (VWF), which is essential for normal haemostasis[2]. VWF binds factor VIII, a key clotting protein, and platelets in blood vessel walls, which help form a platelet plug during the clotting process. People with VWD are not able to form this platelet plug, or it will take longer to form[2]. VWD is the most common hereditary blood clotting disorder and classified into six types (1, 2A, 2B, 2M, 2N and 3); patients, especially those with type 3 and some type 2 variants, have an increased risk of experiencing potentially life-threatening bleeding[3]. It is believed to affect up to 1% of the population, while symptomatic prevalence is likely closer to 0.1%[4]. There were 2,029 people under 18 years old registered with VWD in the UK between 2020 and 2021[5]. Only 34 cases in Wales were recorded on the Congenital Anomaly Register and Information Service (CARIS) database between 1998 – 2015, which is lower than the estimated prevalence but may be due to under-reporting and many cases going undiagnosed[6]. Clinical experts have estimated that 104 children with VWD are eligible to receive treatment with vonicog alfa in Wales. Routine testing of infants before the age of 6 months is not recommended because there are natural changes in the presence of VWF in the blood in the early months of life[6].

The symptoms of VWD may start at any age. They can range from very mild and barely noticeable to frequent and severe. The main symptoms are: large bruises or bruising easily, nosebleeds, bleeding gums, heavy or long-lasting bleeding from lacerations and procedures, and menorrhagia. People with VWD are at increased risk of developing anaemia and gastrointestinal bleeding[7].

Current treatment options and relevant guidance

There is currently no cure for VWD[8]. Clinical practice recommendations for diagnosis, treatment and follow-up were published in 2014 by the United Kingdom Haemophilia Centre Doctors Organisation (UKHCDO)[9]. The aim of treatment is to correct the clotting process and reduce the extended bleeding time in people with VWD[2]. Currently treatment options include desmopressin, tranexamic acid, and products made from human blood containing either high purity VWF alone or intermediate purity VWF with factor VIII. Patient-specific management depends on type and severity of the condition and bleed[2].

Desmopressin works by temporarily boosting endogenous factor VIII and VWF and is only effective in some patients with VWD (e.g. less severe type 1 VWD)[2]. Desmopressin is contraindicated in people with cardiovascular disease, and fluid restriction is necessary to avoid hyponatremia and the risk of seizures, especially in young children. It has been linked to thrombocytopenia in type 2B VWD[10]. Antifibrinolytic treatment (tranexamic acid) works by stopping the breakdown of clots

and is often used as adjunctive therapy for treating minor bleeding or used before surgery[2].

Plasma-derived products are made using human blood and commonly contain both VWF and factor VIII to help clotting[2]. They are used for preventing and treating bleeding in major surgery or for treating serious bleeding episodes. A number of plasma-derived concentrates containing VWF are available for replacement therapy in patients whose desmopressin response is inadequate, however there are disadvantages compared to artificially made alternatives which are not dependent on donor availability. These products can also vary in their effectiveness due to natural differences in the VWF protein found in human blood. In addition, plasma-derived products contain extraneous plasma proteins that may engender allergic responses, which are sometimes severe and may limit their use[11]. Plasma-derived products used in the UK have an excellent recent safety history though there remains a theoretical risk of plasma-borne pathogen transmission[2].

Clinical evidence

The evidence of clinical efficacy of vonicog alfa comes mainly from two clinical trials in the adult population (>18 years)[3,12]. A case study found from the literature search reported the first use of vonicog alfa in a paediatric patient. There are currently two clinical trials underway in the paediatric population with estimated completion in 2023 and 2025[13,14]. Other supporting documents are presented in Table 3.

Gill et al. (2015) conducted a part-randomised, open label study designed to assess the pharmacokinetics (PK), safety, and haemostatic efficacy of vonicog alfa (rVWF) in the treatment of bleeding episodes (BEs) in adults with severe VWD[3]. A total of 37 patients (median age 37 years) were enrolled into one of four arms, at the investigator's discretion, to receive rVWF for PK assessment and/or 6-12 months of on-demand treatment of BEs. rVWF was initially administered together with recombinant factor VIII (rFVIII) and then subsequently alone as long as haemostatic factor VIII activity (FVIII:C) levels were maintained.

The primary efficacy outcome was assessed using a pre-defined 4-point rating scale to score haemostatic efficacy with 1 indicating excellent, 2 (good), 3 (moderate), and 4 (none)[3]. Efficacy rating criteria used to estimate the score included the actual number of rVWF infusions required versus the treating clinician's estimate and whether additional VWF-containing coagulation product was needed[3].

The primary endpoint of the study was the number of subjects with a treatment success for treated BEs during the 12-month study[3]. Treatment success was defined as a mean haemostatic efficacy rating score of <2.5. Secondary endpoints included the number of treated BEs with an efficacy rating of 'excellent' or 'good' and the number of infusions and number of units of rVWF:rFVIII and/or rVWF per BE[3].

Number of subjects with a treatment success for treated BEs during the 12-month study: overall the treatment success rate was 100% and suggested that all participants had an excellent or good control[3]. All participants who experienced 1 or more bleeding episodes treated with vonicog alfa in the study (n = 22) reported an efficacy score of less than 2.5, with an overall treatment success rate of 100% (Clopper-Pearson exact 90% confidence interval [CI]: 87.3 to 100.0%). The results suggest that all participants had excellent or good control of bleeding episodes with vonicog alfa (with or without rFVIII)[3,15].

Number of treated BEs with an efficacy rating of excellent or good: This outcome looked at how many of the BEs controlled by vonicog alfa (with or without rFVIII) were rated as excellent or good[3]. A total of 192 bleeding episodes (minor: n = 122, moderate: n = 61, major/severe: n = 7 and unknown severity: n = 2) in 22 participants were treated successfully (100%; Clopper-Pearson exact 95% CI: 98.1 to 100%), with results rated as excellent in 96.9% and good in 3.1% of bleeds. The cause of bleed appeared not to have an impact on efficacy, with excellent efficacy ratings in 97.5% (160/165) of spontaneous and 100% (26/26) of traumatic bleeds[3,15].

Number of infusions and units of vonicog alfa/rFVIII and/or vonicog alfa per bleeding episode: This outcome looked how many infusions and units (or dose) were needed to stop a BE based on the severity and location of the bleed[3]. Most bleeds (81.8%, [157/192]) were stopped by a single infusion (median 1 infusion, range 1 to 4 infusions). The median dose of vonicog alfa and rFVIII administered per bleed was 46.5 IU/kg (range 23.8 to 139.6 IU/kg and 33.6 IU/kg (range 16.6 to 129.3 IU/kg), respectively[3,15,16]. One bleed (in the genital tract and oral cavity concomitantly, participant with type 3 VWD) required 4 infusions, which was the maximum number of infusions administered to treat a bleed during the study. A median of 2 infusions (range 1 to 3) was required to control major bleeds. The amount of vonicog alfa administered per bleed was generally higher for bleeds of greater severity[3,15].

Peyvandi et al. (2018) conducted a prospective, non- comparative, non- randomised open- label phase III study evaluating the haemostatic efficacy and safety profile of vonicog alfa (rVWF), with or without rFVIII, in patients with severe VWD undergoing planned elective surgery[12]. Fifteen patients (median age 40) at 12–24 hours before surgery were given rVWF 40–60 IU/kg VWF:RCo intravenously to allow endogenous FVIII:C levels to rise to ≥ 30 IU/dL^{-1} (minor/oral surgery) or ≥ 60 IU/dL^{-1} (major surgery), which were to be assessed within 3 hours of initiation of the surgery. If target FVIII:C levels were achieved, rVWF alone was administered within 1–2 hours before surgery to achieve peak levels. If target FVIII:C levels were not achieved, rVWF was co-administered with rFVIII within 1–2 hours before surgery to meet recommended peak levels[12].

The primary outcome measure included overall investigator-assessed haemostatic efficacy of rVWF at 24 hours after the last perioperative infusion or on completion of the study by using a four-point rating scale (1 = excellent, 2 = good, 3 = moderate or 4 = none) based on haemostasis relative to a haemostatically normal subject without VWD. Intraoperative haemostatic efficacy was assessed by the surgeon using the same scale and intraoperative actual versus predicted blood loss was also surgeon evaluated.

Both overall and interoperative haemostatic efficacy were rated as ‘excellent’ or ‘good’ in 100% of patients (n = 15/15: 90% CI, 81.9 to 100). For patients with type 3 VWD both the overall and intraoperative haemostatic efficacy were rated as ‘excellent’ (n = 7/8) or good’ (n = 1/8). Patients received a total of 104 surgical infusions of rVWF: 93 infusions (89.4%) of rVWF alone and 11 infusions (10.6%) in five patients administered with rFVIII (see Table 2.). Haemostatically effective levels of endogenous FVIII were reached within six hours and were sustained for 72–96 hours; 70% (n = 7/10) of major surgeries were performed without rFVIII co-administration[12].

Table 1. Treatment summary of all bleeding episodes[3]

	No. bleeding episodes	Total no. infusions	Median (range) no. infusions/bleed	Median (range) VWF:RCo dose (IU/kg)/infusion	Median (range) rFVIII dose (IU/kg)/infusion	% bleeds (n = 192) rated excellent or good (n excellent/good)
Subject VWF type						
Type 3	175	219	1 (1-4)	48.2 (23.8-184.9)	33.6 (16.6-129.3)	100% (171/4)
Type 2A	16	18	1 (1-2)	50.2 (32.9-90.2)	32.5 (23.7-38.6)	100% (14/2)
Type 2N	1	1	1 (1-1)	54.3 (54.3-54.3)	NA	100% (1/0)
Bleed severity						
Minor	122	132	1 (1-3)	43.3 (25.2-158.2)	33.5 (17.6-86.2)	100% (119/3)
Moderate	61	89	1 (1-4)	52.7 (23.8-184.9)	36.9 (16.6-129.3)	100% (59/2)
Major/severe	7	15	2 (1-3)	100.0 (57.5-135.0)	39.0 (25.0-42.3)	100% (6/1)
Unknown	2	2	1 (1-1)	33.4 (33.1-33.8)	23.3 (23.1-23.6)	100% (2/0)
Bleed site						
Joint	59	66	1 (1-3)	48.2 (23.8-139.6)	34.9 (16.6-129.3)	100% (57/2)
Gastrointestinal	6	10	1 (1-2)	60.0 (53.6-121.1)	33.2 (19.3-49.4)	100% (5/1)
Mucosal	106	121	1 (1-4)	43.3 (23.8-184.9)	30.6 (16.6-61.3)	100% (103/3)
Other	37	57	1 (1-4)	52.2 (25.2-184.9)	36.8 (17.6-86.2)	100% (36/1)
Bleed cause						
Spontaneous	165	255	1 (1-4)	46.5 (23.8-184.9)	33.6 (16.6-86.2)	100% (160/5)
Traumatic	26	30	1 (1-3)	51.9 (25.2-139.6)	35.8 (17.6-129.3)	100% (26/0)
Unknown	1	3	3 (3-3)	125.5 (125.5-125.5)	50.3 (50.3-50.3)	100% (0/1)

rFVIII: human recombinant FVIII; VWF: von Willebrand factor; VWF:RCo: von Willebrand factor: ristocetin cofactor activity

Table 2. Surgical infusions of rVWF and rFVIII[12]

Time of infusion	Number of infusions with rVWF alone	Number of infusions with rVWF and rFVIII	Number of total infusions
12–24 h before surgery	15	0	15
1 h before surgery	12	3	15
Intraoperative	0	1	1
Postoperative (0–14 days)	66	7	73
Total infusions, n (%)	93 (89.4)	11 (10.6)	104 (100.0)

Weyand et al (2018) reported the first use of rVWF in a paediatric patient. A 2-year-old child underwent multiple procedures over several days due to skull fracture and large epidural haemorrhage after a fall. Use of a plasma-derived FVIII/VWF concentrate was deemed to pose an unacceptable risk of thrombosis. The rVWF (80 IU/kg) was administered just prior to surgery. Adequate haemostasis was achieved with minimal blood loss. Due to a drop in haemoglobin on postoperative day 2 there was concern of an acute bleed and so an additional dose of 80 IU/kg rVWF was administered. This observation was later attributed to dilutional effects of intravenous fluid, and no evidence of bleeding was found by clinical assessment or imaging[17].

Table 3. Relevant publications found in literature search

Reference	Study details	Main results
Desprez et al. (2021)[18]	This multicentre retrospective study reports real-world data of 63 surgeries for 55 patients (median age 44 years). For each patient, the doses and times of rVWF infusion were adjusted at the discretion of the investigator according to the clinical situation. A rFVIII product was administered with the first infusion of rVWF if the patient's baseline plasma FVIII:C level was <40 IU/dL. The efficacy in achieving haemostasis was evaluated by haematologists who enrolled patients according to the international ISTH criteria (Excellent, Good, Moderate, Poor).	During minor surgeries, the median (range) number of infusions was 1 (1–8) with a preoperative loading dose of 35 (19–56) rVWF IU/kg and a total median dose of 37.5 IU (12–288). During major surgeries, the median (range) number of infusions was only 3 (1–14) with a median preoperative loading dose of 36 IU (12–51) rVWF IU/kg, and a total median dose of 108 IU (22–340) rVWF IU/kg. The overall clinical efficacy was qualified as excellent/good in 61 of the procedures (97%), moderate in 1 (1.5%) and poor in 1 (1.5%). There was no accumulation of VWF or FVIII during postoperative monitoring. No thromboembolic events, anti-VWF antibodies or adverse events were reported.
Genre Volot et al. (2020)[19]	This abstract reports real-world data of ten surgical procedures in eight patients aged between 36 and 73 years. rVWF was administered at 32-48 IU/kg1-2 hours before procedure. All minor surgeries were managed with one rVWF infusion (average dose 30.2 IU/kg). No FVIII infusion was needed in any patient; all type 1 patients had baseline FVIII activity (FVIII:C) ≥49%; the type 3 patient received one infusion of rVWF 12 hours before procedure, allowing endogenous FVIII:C to rise > 50%.	VWF parameters measured 24 hours post-surgery were consistent with expectations. Tolerance was overall excellent, no allergic reactions, bleeding or thromboembolic events were reported. Low molecular weight heparin was administered during 10 days after gastric bypass, with an uneventful follow-up.
Gao et al. (2019)[20]	This poster abstract presents data from indirect treatment comparisons between recombinant VWF (rVWF, vonicog alfa) and 3 commonly used plasma derived VWF concentrates, using patient-level data including data from Gill et al. 2015. The analysis endpoint was the ‘number of infusions’ required to stop a bleed.	Using data on 192 bleeds for rVWF, results of the comparison of number of infusions needed to stop a bleed, adjusting for daily dose, are presented. All comparisons for means and the majority of comparisons for medians showed a lower number of rVWF infusions were needed to stop a bleed. Other comparisons on medians were equivocal, possibly due to discreteness. The indirect treatment comparisons indicate fewer infusions of rVWF compared to plasma-derived VWF may be needed to control a bleed. Several assumptions and limitations of the analysis are noted; e.g., assessments and treatment decisions in different studies were assumed to be comparable. Despite these limitations, the data generated suggest the potential value of VWD bleed treatment with rVWF.

Safety

The European Medicines Agency public assessment report (EPAR) states that overall, a sufficient number of adult participants have been exposed to vonicog alfa for the treatment of bleeding episodes with a total duration of 12 months, during surgical procedures and for pharmacokinetic assessments, to adequately evaluate the safety profile[15,16]. Eighty unique subjects (four completed clinical trials) included in the safety analysis set are considered acceptable to constitute a solid database for common AEs such as hypersensitivity related reactions. However, the population is too small to adequately address rare unfavourable effects, i.e. inhibitor formation and thromboembolic events. Post-marketing data are required to address these uncertainties. Most of the reported adverse events are expected for treatment with VWF products or blood coagulation factors, and were mostly regarded as infusion or hypersensitivity reactions. Most of the treatment-related adverse events reported in the studies were mild to moderate in severity[15,16]. The SPC for vonicog alfa highlights the following adverse reactions may occur: hypersensitivity or allergic reactions, thromboembolic events and inhibitor formation against VWF[1].

In the Gill et al. trial, eight of a total 125 adverse events (AEs; 6.4%) observed were considered to have a causal relationship to rVWF[3]. Six of these AEs in four subjects were not serious. One subject experienced mild infusion site paraesthesia, moderate dysgeusia and moderate tachycardia, one subject showed a mild ECG T-wave inversion, one subject experienced mild generalised pruritus, and one subject had a mild hot flush. One subject experienced two simultaneous serious AEs (chest discomfort and increased heart rate). These symptoms improved after 10 minutes of oxygen treatment, the subject fully recovered within three hours, and no clinical cardiac symptomatology was observed. This AE was assessed as serious due to hospitalisation for the purpose of observation. The subject had a history of allergic responses to cryoprecipitate and a plasma-derived VWF concentrate.[3]

A total of 12 treatment-emergent AEs was reported in six patients in the Peyvandi et al. trial, including acne, anaemia, deep vein thrombosis (DVT), diverticulitis, dizziness, dry skin, headache, joint swelling, nasopharyngitis, pelvic pain and peripheral swelling[12]. Among them, two patients had serious AEs (one with diverticulitis and one with DVT). None of these events were considered treatment related by the investigator. One participant with type 3 VWD had a positive result for anti-VWF binding antibodies, but no adverse events were reported. The authors report that these antibodies were non-inhibitory and had no effect on vonicog alfa[12].

There were no reported deaths, severe allergic reactions or discontinuations in either study. There were also no other findings of thromboembolic events, anti-VWF neutralising or binding antibodies, factor VIII neutralising antibodies, or antibodies against rFurin, Chinese hamster ovary host cell proteins, or murine immunoglobulin G.

No adverse events were reported for the sole paediatric patient treated with rVWF described by Weyand et al. The patient recovered well without complication, with no thrombotic complications, and no evidence of antibodies to VWF was observed[17]. Overall the safety profile of this treatment in children is unknown.

Discussion

- Vonicog alfa (Veyvondi®) is the only recombinant VWF developed for substitution therapy in VWD disease. Welsh clinical experts indicate there is an unmet medical need for alternative therapies to the current plasma-derived blood products used which have a theoretical risk of transmission of plasma-borne pathogens.
- No studies for efficacy and safety have been carried out in children. In this report we present the evidence submitted to the EMA to obtain a licence in adult use. Phase III clinical trials in the paediatric cohort are ongoing. There is only one reported use of rVWF in a paediatric patient[17]. Clinical experts state therapeutic response to vonicog alfa in children is expected to be similar to that in adults. Dosing of vonicog alfa is based on body weight and the desired increment in the von Willebrand function for all patients.
- If administered without FVIII, it was shown that vonicog alfa increased endogenous FVIII levels substantially reaching elimination kinetics similar to when co-administered with rFVIII[16].
- No comparative, randomised controlled trials comparing infusion requirements between rVWF and plasma-derived VWF concentrates have been performed[20]. Data from indirect treatment comparisons using patient-level data has been published as a poster abstract. The abstract is not peer reviewed and contains several assumptions and limitations including assessments and treatment decisions from different studies[20].
- Both main studies included in this report have limitations including open label, small sample size, use of concomitant medication, retrospective efficacy assessment and statistical issues. Gill et al was a non-comparative study and therefore does not provide evidence that vonicog alfa is any better or worse than other treatments for this outcome. Peyvandi et al was neither randomised or blinded. Outcomes were assessed subjectively, which may have introduced investigator or surgeon bias. However, the possible methodological flaws are considered not likely to have a qualitative impact on the primary efficacy assessment[16].
- Both studies included people with severe VWD who previously needed plasma-derived VWF, and most (but not all) included people with type 3 VWD. Therefore, results are limited to these populations who need plasma-derived VWF. There was no quality of life outcomes reported in the studies.

Cost-effectiveness evidence

No studies on the cost effectiveness of vonicog alfa were identified for the adult or paediatric populations.

Budget impact

The pathway shown in Appendix 1 is taken from the WHSSC commissioning policy PP215 and outlines that vonicog alfa will be available as a second line treatment, given when desmopressin treatment with or without tranexamic acid is ineffective or not indicated. Plasma-derived VWF is current standard of care at second line, and it remains a treatment choice at this point in the pathway[21]. Clinical experts state paediatric use will remain consistent with this approach.

Clinical experts have indicated that vonicog alfa would be used as a single treatment for a major bleed in patients aged 0 to 17 years with an estimated uptake of 20 patients per annum in Wales. Vonicog alfa should be administered with recombinant factor VIII if the FVIII:C levels are < 40%, or are unknown, to control bleeding[1]. Dose received is calculated based on weight in kg. The comparator, and therefore the displaced medicine, is plasma-derived VWF (Voncento®) which contains FVIII and VWF as active ingredients. In the absence of any consensus and guidelines, dosage is to be based on the median dosage reported by Gill et al (median dose of rVWF and rFVIII administered per bleed was 46.5 IU/kg VWF:RCo and 33.6 IU/kg, respectively)[3]. This guidance matches the lower limit in the SPC[1].

Given approximate average weights of 3kg to 64kg for a child from birth to 17 years[22], the number of vials need for a single treatment would range from 1 to 5. Using an assumed average weight of 28kg (the average weight of a 9-year-old child)[22], calculated treatment costs for vonicog alfa (Veyvondi®) and plasma-derived VWF (Voncento®) are presented in Table 4. These are based on a required dose of 1302IU vonicog alfa and 940.8IU rFVIII following the median dosage used by Gill et al[3].

Treatment is assumed to be a single treatment given on demand, and no patients carry on treatment into the following year. The commercially discounted price agreed between the company and NHS Wales for vonicog alfa (Veyvondi®) is [commercial in confidence text removed] for 650IU vial and [commercial in confidence text removed] for 1300IU vial (excluding VAT). Some vial wastage is assumed.

Table 4. Estimated annual acquisition costs in Wales

	vonicog alfa (Veyvondi®)*†§	plasma derived VWF (Voncento®) *†¶
Net drug acquisition costs	¶¶	£770
Net additional VWF:RCo costs**	£710	£0
Overall net cost per patient	¶¶	**£770**

* This assumes patient weighs 28kg, average weight of a nine-year-old.
† This assumes a single on demand treatment.
§ Assumes one 1300IU vial at the agreed commercially discounted price of [commercial in confidence text removed] per vial
¶ Assumes one 1000IU/2400IU vial at £770 per vial[23]
** Assumes one 1000IU vial rFVIII (Advate®) at £710 per vial[23]
¶¶ Commercial in confidence figure removed

Table 5 shows the net budget impact assuming that all eligible patients receive vonicog alfa (Veyvondi®) instead of the comparator.

Table 5. Estimated net cost in Wales

	Year 1	Year 2	Year 3
Number of people eligible for treatment	**20**	**20**	**20**
Total costs for plasma-derived VWF (Voncento®) per year	£15,400	£15,400	£15,400
Total costs for vonicog alfa (Veyvondi®) per year	¶¶	¶¶	¶¶
Net cost assuming 100% displacement of comparator	¶¶	¶¶	¶¶

Discussion:

- The budget impact is based on drug acquisition costs only and therefore does not consider administration and monitoring costs, hospitalisation costs, adverse event costs or any additional palliation costs. However, it can be assumed that these additional costs will be similar for treatment with either vonicog alfa or the plasma-derived VWF comparator.
- The budget impact assumes that all eligible patients are co-administered rFVIII. In practice, this is only necessary when patient FVIII:C levels are < 40%, or are unknown; thus, the total cost for vonicog alfa treatment may be reduced due to no rFVIII acquisition costs for some patients.
- The number of patients expected to receive Veyvondi® and the dosing used in the analysis are subject to uncertainty. The number of patients per year is likely to remain stable as the older children move in to WHSSC-commissioned adult services for their treatment. Dosing of vonicog alfa is individualised and based on patient body weight and the desired increment in the von Willebrand function. The estimate has been made using the average weight at the mid-point age of the paediatric indication (four 9-year-olds). AWTTC consider a higher budget impact than that estimated is plausible.
- The company suggests that real world usage in adults indicates lower dosing is required to that recommended in the SPC and, therefore, the estimated budget impact may be reduced.

Additional factors

Prescribing unlicensed medicines

Vonicog alfa (Veyvondi®) is not licensed to treat this indication and is therefore 'off-label'. Providers should consult the relevant guidance on prescribing unlicensed medicines before any off-label medicines are prescribed.

Information presented in this document can be reproduced using the following citation: All Wales Therapeutics & Toxicology Centre. Evidence Status Report. vonicog alfa (Veyvondi®▼) for the on-demand treatment of non-surgical and surgical (elective and emergency) bleeding episodes in children aged up to 17 years with severe von Willebrand disease (OW19). 2022.

References

1. Takeda UK Ltd. VEYVONDI®. Summary of Product Characteristics. September 2021. Available at: https://www.medicines.org.uk/emc/product/11233/smpc#gref. Accessed July 2022.
2. NHS England. Clinical Commissioning Policy: Vonicog alfa for the treatment and prevention of bleeding in adults with von Willebrand disease. 200801P [1709]. Available at: www.england.nhs.uk/wp-content/uploads/2020/09/1709-cc-policy-vonicog-alfa-for-von-willebrand-disease.pdf. Accessed July 2022.
3. Gill JC, Castaman G, Windyga J et al. Hemostatic efficacy, safety, and pharmacokinetics of a recombinant von Willebrand factor in severe von Willebrand disease. *Blood.* 2015;126(17):2038-2046.
4. Sidonio RF, Weyand AC, Cheng D et al. Assessing the Safety of Various VWF Regimens in Patients with Clinically Severe VWD: A Natural History Study. *Blood.* 2019;134:1132.
5. United Kingdom Haemophilia Centre Doctors' Organisation. UKHCDO Annual Report 2020 & Bleeding Disorder Statistics for 2020/2021. 2021. Available at: www.ukhcdo.org/wp-content/uploads/2021/12/2021-UKHCDO-Annual-Report-2020-21-Data.pdf. Accessed July 2022.
6. Public Health Wales. Von Willebrand Disease. Available at: https://phw.nhs.wales/services-and-teams/caris/key-anomalies/blood-disorders/#Von%20Willebrand%20disease. Accessed July 2022.
7. National Health Service. Von Willebrand disease. 2020. Available at: https://www.nhs.uk/conditions/von-willebrand-disease/. Accessed July 2022.
8. The Haemophilia Society. Von Willebrand Disorder. Available at: https://haemophilia.org.uk/bleeding-disorders/von-willebrand-disease/. Accessed July 2022.
9. Laffan MA, Lester W, O'Donnell JS et al. The diagnosis and management of von Willebrand disease: A United Kingdom Haemophilia Centre Doctors Organization guideline approved by the British Committee for Standards in Haematology. *British Journal of Haematology.* 2014;167(4):453-465.
10. Miesbach W, and Berntorp E. Von Willebrand disease - the 'Dos' and 'Don'ts' in surgery. *The European Journal of Haematology.* 2017;98(2):121-127.
11. Ofosu FA, Freedman J, and Semple JW. Plasma-derived biological medicines used to promote haemostasis. *Thrombosis and Haemostasis.* 2008;99(5):851-862.
12. Peyvandi F, Mamaev A, Wang JD et al. Phase 3 study of recombinant von Willebrand factor in patients with severe von Willebrand disease who are undergoing elective surgery. *Journal of Thrombosis and Haemostasis.* 2019;17(1):52-62.
13. Takeda UK Ltd. NCT02932618: A Study of Recombinant Von Willebrand Factor (rVWF) With or Without ADVATE in Children With Severe Von Willebrand Disease (VWD). April 2022. Available at: https://clinicaltrials.gov/ct2/show/NCT02932618. Accessed July 2022.
14. Takeda UK Ltd. NCT03879135: A Study of Recombinant Von Willebrand Factor (rVWF) in Pediatric and Adult Participants With Severe Von Willebrand Disease (VWD). April 2022. Available at: https://clinicaltrials.gov/ct2/show/NCT03879135. Accessed July 2022.
15. NICE clinical evidence review for vonicog alfa for treating von Willebrand disease. URN1709 / NICE ID018. March 2020. Available at: www.england.nhs.uk/wp-content/uploads/2020/09/1709-vonicog-alfa-evidence-review.pdf.
16. European Medicines Agency. Assessment Report: VEYVONDI®. Procedure No.: EMEA/H/C/004454/0000. June 2018. Available at: www.ema.europa.eu/en/documents/assessment-report/veyvondi-epar-public-assessment-report_en.pdf. Accessed July 2022.

17. Weyand AC, Jesudas R, and Pipe SW. Advantage of recombinant von Willebrand factor for peri-operative management in paediatric acquired von Willebrand syndrome. *Haemophilia.* 2018;24(3):e120-e121.
18. Desprez D, Drillaud N, Flaujac C et al. Efficacy and safety of a recombinant Von Willebrand Factor treatment in patients with inherited Von Willebrand Disease requiring surgical procedures. *Haemophilia.* 2021;27(2):270-276.
19. Genre Volot F CA, de Maistre E,. Recombinant von Willebrand Factor (rVWF) in Patients with von Willebrand Disease (VWD) Undergoing Elective or Emergency Surgery in Real World Setting – The Dijon University Hospital Experience from March 2019 to January 2020 [abstract]. *Research and Practice in Thrombosis and Haemostasis.* 2020;4(1).
20. Gao J, Ewenstein B, Ploder B et al. Infusion requirements in on demand treatment of bleeding events in Von Willebrand disease (VWD): An indirect treatment comparison between recombinant Von Willebrand factor (VWF) and plasma derived VWF concentrates. *Research and Practice in Thrombosis and Haemostasis.* 2019;3(Supplement 1):391.
21. The Welsh Health Specialised Services Committee (WHSSC). PP125 Vonicog alfa for the treatment and prevention of bleeding in adults with von Willebrand disease 2021. Available at: https://whssc.nhs.wales/commissioning/whssc-policies/all-policy-documents/vonicog-alfa-for-the-treatment-and-prevention-of-bleeding-in-adults-with-von-willebrand-disease-policy-position-statement-pp215-may-2021/. Accessed July 2022.
22. On Average. Average Child Weight. Available at: https://www.onaverage.co.uk/body-averages/average-child-weight. Accessed Septemer 2022.
23. Haymarket Publications. Monthly Index of Medical Specialities (MIMS). 2022. Available at: http://www.mims.co.uk/. Accessed July 2022.

Appendix 1. Patient pathway

This pathway has been taken from the WHSCC Policy Position Statement: PP125 Vonicog alfa for the treatment and prevention of bleeding in adults with von Willebrand disease[21].