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Newcastle University

Health Technology Briefing
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Vonicog alfa for Prophylaxis of Haemorrhage in Von Willebrand disease

Company/Developer	Takeda UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 24096	NICE TSID: 10266	UKPS ID: 655394

Licensing and Market Availability Plans

The company's regulatory procedure with the MHRA is currently unknown. The company anticipate submitting a Type II major variation to the MHRA in **Q1 2024**, with a final licence expected in and a UK launch expected in **Q2 2025**.

Summary

Vonicog alfa is currently in clinical development for the prevention (prophylaxis) of bleeding episodes in patients with von Willebrand disease (VWD). VWD is a genetic bleeding disorder caused by a deficiency or absence of a blood clotting factor, called the von Willebrand factor. This causes poor blood clotting, which results in difficulty in stopping the flow of blood from a wound, causing prolonged bleeding. Current therapy includes preventative (prophylactic) treatment where medicine is used to prevent bleeding, or on-demand treatment, where medicine is used to treat prolonged bleeding.

Vonicog alfa is an intervention that behaves as the natural von Willebrand factor in order to counteract the deficiency and reduce the prolonged bleeding time in people with VWD. Vonicog alfa is administered as an intravenous (IV) injection. There is currently no cure for VWD, despite it being one of the most commonly inherited bleeding disorders. If approved, Vonicog alfa will provide a novel treatment option for the prophylaxis of adult patients with VWD.

Proposed Indication

Prophylaxis of haemorrhage in adults with VWD, when desmopressin (DDAVP) treatment alone is ineffective or not indicated.[a]

Technology

Description

The recombinant human von Willebrand factor (rVWF, Veyvondi, Vonicog alfa) behaves in the same way as endogenous von Willebrand factor. Administration of rVWF allows correction of the haemostatic abnormalities exhibited by patients who suffer from von Willebrand factor deficiency (von Willebrand's disease) at two levels:[1]

- Vonicog alfa 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.

- Vonicog alfa produces delayed correction of the associated factor VIII deficiency. Administered intravenously, rVWF 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 rVWF restores the FVIII:C level to normal as a secondary effect after the first infusion.

Vonicog alfa is currently in clinical development for the prevention (prophylaxis) of bleeding episodes in patients with von Willebrand disease (VWD). . In the phase III clinical trial, patients were given IV infusions of rVWF with an initial dose of 50 +/- 10 VWF:RCo International Units per Kilogram (IU/kg) twice a week for at least 12 months, up to 15 months. If license extension is granted, vonicog alfa would be a treatment option for the prophylaxis of bleeding for adult patients with VWD.[2]

Key Innovation

Patients with VWD, especially those with the severe bleeding phenotype, have a poorer health-related quality of life than the general population and are at increased risk of bleeding, which can be life-threatening (e.g., gastrointestinal events) or lead to long-term complications (e.g., arthropathy). These bleeding events (BEs) require immediate on-demand and/or long-term VWF prophylaxis to induce and/or maintain haemostatic levels of VWF and FVIII. Vonicog alfa is the only recombinant von Willebrand Factor product, other von Willebrand Factor products are plasma-derived Findings suggest that vonicog alfa prophylaxis can reduce the frequency of treated spontaneous bleeding events (BEs) vs historical spontaneous bleeding events, in patients previously receiving on-demand VWF therapy and maintains at least the same level of haemostatic control in patients who switch from prophylaxis with plasma-derived VWF to rVWF, with a favourable safety profile.[3]

Regulatory & Development Status

Vonicog alfa currently has Marketing Authorization in the UK for in adults (age 18 years and older) with VWD, when desmopressin (DDAVP) treatment alone is ineffective or not indicated for the following:[1]

[a] Information provides by Takeda UK Ltd on UK PharmaScan

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

Patient Group

Disease Area and Clinical Need

Von Willebrand disease (VWD) is a common inherited condition that can make you bleed more easily than normal.[4] It occurs as a result of decrease in plasma levels or quantitative defect in VWF which is a large multimeric glycoprotein. Monomers of this glycoprotein undergo N-glycosylation to form dimers which get arranged to give multimers. Binding with plasma proteins (especially factor VIII) is the main function of von Willebrand factor. The management of the disease involves replacement therapy, non-replacement therapy and other therapies that include antifibrinolytics.[5]

The main symptoms are: large bruises or bruising easily, frequent or long-lasting nosebleeds, bleeding gums, heavy or long-lasting bleeding from cuts, in women, heavy periods and heavy bleeding during or after labour and heavy or long-lasting bleeding after a tooth removal or surgery. In some people, there's also a small risk of problems such as bleeding in the gastro-intestinal tract and painful bleeds into joints and muscles.[4]

There are several types of VWD. The main types are:[4]

- type 1 – the mildest and most common type. People with type 1 VWD have a reduced level of von Willebrand factor in their blood. Bleeding is mostly only a problem if you have surgery, injure yourself, or have a tooth removed.
- type 2 – in people with this type of VWD, von Willebrand factor does not work properly (qualitative deficiency). Bleeding tends to be more frequent and heavier than in type 1.
- type 3 – the most severe and rarest type. People with type 3 VWD have very low levels of von Willebrand factor, or none at all. Bleeding from the mouth, nose and gastrointestinal-tract is common, and you can have joint and muscle bleeds after an injury.

These 3 types are all inherited. There is also a rare type that is not inherited called acquired von Willebrand disease. This can start at any age and is usually associated with other conditions that affect the blood, immune system or heart.[4]

VWD is the most common inherited bleeding disorder. It is thought around one per cent of the UK population have reduced levels of VWF, but this is rarely severe enough to cause problems or require treatment. [6] It affects slightly more women than men; with 7,071 women and 4,081 men diagnosed in the UK (though many thousands remain undiagnosed).[7] In England (2021-22), there were 1,567 finished consultant episodes (FCE) and 1,532 admissions for Von Willebrand disease (ICD-10 code D68.0) which resulted in 448 FCE bed days and 1,336 day cases.[8]

Recommended Treatment Options

There is currently no NICE recommended treatment options for VWD.

There are three main medicines that can help with controlling bleeds in VWD:[4]

- desmopressin – available as a nasal spray or injection
- tranexamic acid – available as tablets, a mouthwash or an injection

- Plasma-derived von Willebrand factor concentrate – available as an injection
- Recombinant von Willebrand factor concentrate – available as an injection.

However, Vonicog alfa is recommended via the NHSE CPAG route for the treatment of haemorrhage and surgical bleeding and the prevention of surgical bleeding.[b]

Clinical Trial Information	
Trial	NCT02973087, EudraCT2016-001478-14; A PROSPECTIVE, PHASE 3, OPEN-LABEL, INTERNATIONAL MULTICENTER STUDY ON EFFICACY AND SAFETY OF PROPHYLAXIS WITH rVWF IN SEVERE VON WILLEBRAND DISEASE **Phase III:** Completed **Location(s):** 7 EU Countries, UK, US, Canada and other countries **Primary completion date:** July 2020
Trial Design	Single group assignment, open label
Population	N=29 (actual); ages 18 years and older; documented diagnosis of severe von Willebrand disease (VWD); with a history of requiring substitution therapy with von Willebrand factor concentrate to control bleeding, Type 1 (VWF:RCo <20 IU/dL) or, Type 2A (as verified by multimer pattern), Type 2B (as diagnosed by genotype), Type 2M or, Type 3 (Von Willebrand factor antigen (VWF:Ag) less than or equal to [< or =] 3 IU/dL).
Intervention(s)	Vonicog alfa IV infusion
Comparator(s)	N/A
Outcome(s)	**Primary Outcome(s):** • Ratio of Annualized Bleeding Rate (ABR) for Spontaneous Bleeding Episodes (BEs) (On-study ABR / Historical ABR) Assessed by Investigator During Prophylactic Treatment With rVWF Through Month 12 [Time frame: up to 12 months] See trial record for full list of outcomes.
Results (efficacy)	23 enrolled patients received rVWF prophylaxis (prior OD arm: n=13; switch arm: n=10) and 18/23 (78.3%) patients had type 3 VWD. Over the 12-month study period, 11/13 (84.6%) prior OD patients and 7/10 (70.0%) switch patients had a treated, sABR of zero, whereas, historically, 13/13 prior OD and 1/10 switch patients had an sABR >2.[9] See trial record for full results.
Results (safety)	Benefit-risk profile was maintained, with no newly identified risks. One adverse event, a nonserious headache of moderate severity, was considered possibly related to rVWF by the investigator and led to discontinuation of rVWF and study withdrawal.[9]

[b] Information provided by Takeda UK Ltd

	See trial record for full results.

Estimated Cost

Vonicog alfa is already marketed in the UK; a 650 unit powder and solvent for solution for injection vial costs £598 and a 1,300 unit powder and solvent for solution injection vial costs £1,196.[10]
Confidential PAS discount is available.[c]

Relevant Guidance

NICE Guidance

No relevant guidance identified.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Vonicog alfa for the treatment and prevention of bleeding in adults with von Willebrand disease. 2020.

Other Guidance

- American Society of Hematology (ASH), the International Society on Thrombosis and Haemostasis (ISTH), the National Hemophilia Foundation (NHF), and the World Federation of Hemophilia (WFH). Guidelines on the diagnosis of von Willebrand disease. 2021.[11]
- Centers for Disease Control and Prevention (CDC). The Diagnosis, Evaluation and Management of von Willebrand Disease. 2020.[12]

Additional Information

Vonicog alfa is recommended for the treatment of haemorrhage and surgical bleeding and the prevention of surgical bleeding. The proposed license extension in this technology briefing is to extend the recommended use of vonicog alfa so that it can also be used in adults with von Willebrand Disease, when desmopressin treatment alone is ineffective or not indicated for the prevention of haemorrhage (i.e. use in prophylaxis).

Vonicog alfa is already reimbursed through the NHSE CPAG route for the current 3 indications, it would make sense to pursue the same approach for use in prophylaxis, so that the approach for reimbursement is consistent. This would mean all 4 indications for vonicog alfa are reimbursed via the NHSE CPAG route.

The NHS Wales Chief Executives have endorsed the recommendation of the One Wales Medicines Assessment Group (OWMAG) with regard to vonicog alfa which is for on-demand treatment of non-surgical and surgical (elective and emergency) bleeding episodes in children aged up to 17 years with von Willebrand disease.[c]

[c] Information provided by Takeda UK Ltd

References

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11 James PD, Connell NT, Ameer B, Di Paola J, Eikenboom J, Giraud N, et al. ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease. *Blood Advances*. 2021;5(1):280-300. Available from: https://doi.org/10.1182/bloodadvances.2020003265.

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