Clinical Commissioning Policy Proposition: Vonicog alfa for the treatment and prevention of bleeding in adults with von Willebrand disease

Reference: NHS England 1709

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Contents

1 Executive Summary

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain Language Summary

About von Willebrand disease

People with von Willebrand disease (VWD) have a low amount of or missing protein called von Willebrand factor (VWF) in their blood, or this protein doesn't work very well. This means that people with VWD have difficulty forming a blood clot (which is needed to stop bleeding when it occurs), and as a result, they bleed more after events such as injury, childbirth, or during surgery. Symptoms can range from very mild and barely noticeable to frequent and severe, and can include nosebleeds, bleeding from the gums, easy bruising, and heavy menstrual bleeding. VWD has 3 main types (known as VWD types 1, 2, and 3), with differing amounts of severity (NHS choices: von Willebrand disease).

About current treatments

Treatment aims to correct the clotting process and reduce the extended bleeding time in people with VWD. Treatments for stopping and preventing bleeds in people with VWD include tranexamic acid, desmopressin, or products made from human blood containing either VWF alone or VWF with another protein that helps with blood clots (known as factor 8).

Choice of treatment depends on type and severity of the condition and bleed. In some people with VWD who have some working VWF, desmopressin works by temporarily boosting their own factor 8 and VWF. It is used for treating bleeding complications or given before surgery for preventing bleeding. Tranexamic acid works by stopping the breakdown of clots and can be used with other treatments. It is used for treating minor bleeding or used before surgery. Blood-derived products are made using human blood and commonly contain both VWF and factor 8 to help the blood to clot. They are used for preventing and treating bleeding in major surgery or for treating serious bleeding episodes.

Plasma-derived products are effective and have an excellent safety record, however there are disadvantages compared to artificially made alternatives which are not dependent on donor availability. Blood derived products can also vary in their effectiveness to help clotting due to natural differences in the VWF protein found in human blood. Plasma-derived blood products used in the UK have an excellent recent safety history though there remains a theoretical risk of plasma-borne pathogen transmission.

About the new treatment

Vonicog alfa works in the body in the same way as von Willebrand factor made by the body itself, by replacing the protein needed to stop bleeding that is missing or not working. It has been artificially made rather than taking it from plasma. Vonicog alfa may be preferred over products taken from plasma because it is less likely to have the problems highlighted above, and, as factor 8 does not need to be given with every dose of vonicog alfa, it avoids the risk of factor 8 building up in the body (a risk factor for clots). Vonicog alfa is currently licensed only for adults (age 18+ years) and only for short-term episodic use (i.e. ‘on-demand’ to treat bleeding episodes and to prevent and treat bleeding during surgery).

What we have decided

NHS England has carefully reviewed the evidence prepared by NICE to treat von Willebrand disease with vonicog alfa in adults. We have concluded that there is enough evidence to consider making the treatment available.

2 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission vonicog alfa for the treatment and prevention of bleeding in adults with von Willebrand disease.

A final decision as to whether vonicog alfa for the treatment and prevention of bleeding in adults with von Willebrand disease will be routinely commissioned will made by NHS England following a recommendation from the Clinical Priorities Advisory Group.

3 Proposed Intervention and Clinical Indication

Von Willebrand disease (VWD) is an inherited genetic disorder caused by missing or defective von Willebrand factor (VWF), a clotting protein. VWF binds factor 8, a key clotting protein, and platelets in blood vessel walls, which help form a platelet plug during the clotting process (National Haemophilia Foundation: Von Willebrand disease). People with VWD have difficulty forming a blood clot and often have bleeding from the mucous membranes. The symptoms of VWD may start at any age. They can range from very mild and barely noticeable to frequent and severe. Symptoms can include nosebleeds, bleeding from the gums, easy bruising, and heavy menstrual bleeding. People with severe VWD may experience bleeding from joints or soft tissue. This can cause chronic musculoskeletal damage and may require joint replacement surgery. In addition, people with the condition may bleed easily after injury, childbirth, and surgery.

Inherited VWD has been classified as 3 main types (known as VWD types 1, 2, and 3) with differing degrees of severity within all types and inheritance patterns. Type 1 is the mildest and most common type and people with type 1 VWD have a reduced level of VWF in their blood. In people with type 2, VWF doesn't work properly and bleeding tends to be more frequent and heavier than in type 1. Type 2 has 4 subtypes (2A, 2B, 2M and 2N). Type 3 is the most severe and rarest type and people with type 3 VWD have very low levels of VWF, or none at all (NHS choices: von Willebrand disease). In addition to the genetic cause, VWD can be acquired during life (known as acquired von Willebrand syndrome).

Treatment of VWD depends on type and severity of the condition and bleed. Treatment aims to correct the deficiency in the clotting process and reduce the prolonged bleeding time in people with VWD. Minor bleeds such as nosebleeds, small bruises, and minor cuts may not need treatment. In mild cases, people with VWD may only need treatment before undergoing surgery or a dental procedure.

Bleeding can be severe and life-threatening in people with more severe VWD. For example gastrointestinal bleeding from angiodysplasia (enlarged blood vessels within the inner lining of the colon) is a serious and life-threatening complication in older people with VWD. Joint bleeding occurs in a considerable number of severely affected people and can lead to joint disease and reduced joint function (Leebeek et al. 2016). Post-partum haemorrhage frequently occurs in women mainly with type 2A and 2B and type 3 VWD. Most people with VWD will require treatment before surgery. According to Leebeek et al. (2016) people with VWD have a lower health-related quality of life compared with the general population.

For people with VWD, key outcomes include preventing the bleed and a reduced burden of treatment (including faster treatment effectiveness, fewer infusions, or fewer units of treatment). This can reduce the time spent in hospital for managing the bleeding episode or after surgery. Recombinant therapy is preferred to plasma-derived concentrates due to a theoretical advantageous safety profile in respect of plasma-derived pathogens.

The UK Haemophilia Centre Doctors Organisation (UKHCDO) has developed (Laffan et al. 2014) guidelines for the diagnosis and management of VWD. Treatments to stop or prevent bleeds in people with VWD include tranexamic acid, desmopressin or plasma-derived concentrates containing either high-purity VWF alone or intermediate-purity concentrates containing VWF and factor 8.

Vonicog alfa is a purified recombinant human von Willebrand factor that works in the body in the same way as natural VWF. It replaces the missing or defective protein, helping the blood to clot and giving temporary control of bleeding. It is administered as an intravenous infusion for treating on demand bleeding episodes and for preventing and treating bleeding during surgery. Vonicog alfa would be an alternative treatment option to plasma derived concentrates for a person with

VWD. Vonicog alfa is the only recombinant human VWF for adults with VWD. Vonicog alfa is currently licensed only for adults (age 18+ years) and only for short-term episodic use (i.e. 'on-demand' to treat bleeding episodes and to prevent and treat bleeding during surgery). Consequently, the scope of the policy proposition is aligned with the current product license. Therefore, vonicog alfa will not be routinely commissioned for paediatric patients or for routine prophylaxis in patients of any age as these are out of scope of the policy proposition.

4 Definitions

Angiodysplasia - a condition where a number of dilated blood vessels develop within the inner wall of the bowel

Autosomal dominant inheritance - 1 gene that is mutated is inherited from either parent causing a genetic disorder. The phenotype of the disorder is produced by a variant in only one allele of the gene.

Autosomal recessive inheritance - 2 alleles of a gene that have mutated are inherited, with 1 coming from each parent, causing a genetic disorder. Both alleles of the gene must contain a variant in order to produce the phenotype of the disorder

Factor 8 (or factor VIII, FVIII) - a blood clotting protein

Plasma-derived products - derived from human plasma and include von Willebrand factor in combination with factor 8.

Recombinant factor 8 (rFVIII) - FVIII made in a cell line using recombinant DNA techniques (therefore not from human plasma)

Recombinant von Willebrand factor (rVWF) - VWF made in a cell line using recombinant DNA techniques (therefore not from human plasma)

Von Willebrand factor (VWF) - this is a large protein essential for normal haemostasis. It binds to damaged blood vessel walls and captures platelets, to form a platelet plug which is the first step in stopping bleeding. It also binds FVIII and prolongs its survival in the circulation.

von Willebrand factor: ristocetin cofactor - a measure of the platelet binding function of VWF in the presence of ristocetin

Von Willebrand disease (VWD) - the disorder due to a deficiency or functional abnormality of von Willebrand factor

5 Aims and Objectives

This policy proposition considered: vonicog alfa for adults with von Willebrand disease when desmopressin treatment alone is ineffective or not indicated for the:

- treatment of haemorrhage and surgical bleeding
- prevention of surgical bleeding.

The objectives were to:

- Review the evidence for the safety and effectiveness of vonicog alfa
- Define the eligibility criteria for vonicog alfa.
- Define the commissioning arrangements required for vonicog alfa

6 Epidemiology and Needs Assessment

Based on the UK National Haemophilia Database Bleeding Disorder Statistics for April 2017 to March 2018, it is estimated that 7,374 adults have VWD in England. A total of 542 adults were treated with desmopressin or with plasma-derived VWF. Of the adults treated with plasma-derived VWF, around 10% (54) used them for prophylaxis and so would not be eligible for treatment with vonicog alfa. The eligible patient population for vonicog alfa in England is considered equivalent to the adults with all types of VWD who are currently treated with plasma concentrates but excluding those using the concentrates for prophylaxis. This is equivalent to 488 adults.

7 Evidence Base

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of this treatment for the indication.

This evidence review considers the results from 2 phase 3, non-comparative, open-label and prospective studies that included people with severe VWD. Gill et al. (2015) was a part-randomised study which included 37 participants (n=22 for

efficacy) who were given vonicog alfa for treating bleeding episodes. Peyvandi et al. (2018) was a non-randomised study which included 15 participants who were given vonicog alfa for preventing and treating bleeding during surgery. Vonicog alfa was co-administered with recombinant factor 8 in some participants in both studies to ensure haemostasis.

To assess the primary efficacy outcomes both studies used a pre-defined 4-point scale of 1 (excellent), 2 (good), 3 (moderate), or 4 (none). In both studies, an estimated (by the treating physician) number of infusions needed to control the bleed, and also predicted blood loss (based on a similar person who does not have VWD), were used to compare with actual values found in people with VWD, in the studies by Gill et al. (2015) and Peyvandi et al. (2018), respectively. In Gill et al. (2015) a score of 1 indicated excellent control of the bleed if the actual number of infusions were less than or equal to estimated and no additional VWF/coagulation factor containing product needed. A score of 4 indicated no control of the bleeding episode because the bleeding was severe and uncontrolled, or intensity of the bleeding episode had not changed, and additional VWF/coagulation factor containing product was required. In Peyvandi et al. (2018), a score of 1 indicated that the use of vonicog alfa (with/without recombinant factor 8) resulted in excellent control of the bleed, when haemostasis was as good as or better than expected for the type of procedure performed in a 'haemostatically normal' person. A score of 4 indicated no control of bleed in participants despite proper dosing, indicating a need to change recombinant VWF concentrate.

Effectiveness

Evidence from Gill et al. (2015) found that treatment with vonicog alfa was successful in 100% of the participants for stopping the bleeding episode (Clopper-Pearson exact 90% confidence interval [CI]: 87.3 to 100.0%). A total of 192 bleeding episodes were recorded, and vonicog alfa was rated as excellent or good for treating 100% of bleedings (Clopper-Pearson exact 95% CI: 98.1 to 100%). 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 administered per

bleed was 46.5 IU/kg (range 23.8 to 139.6 IU/kg (data taken from European Public Assessment Report [EPAR]). Minimised numbers of treatment infusions/units can reduce treatment burden for patients.

Evidence from Peyvandi et al. (2018) found treatment with vonicog alfa was rated as excellent or good for controlling bleeding in all 15 major and minor surgeries that occurred during the study (100%, 90% CI: 81.9 to 100%).

This evidence suggests that vonicog alfa is effective for stopping bleeding episodes and for stopping and preventing bleeding during surgery in people with VWD.

Safety and tolerability

No deaths, severe allergic reactions or discontinuations were reported in either study. Most of the treatment-related adverse events reported in the studies were mild to moderate in severity.

Gill et al. (2015) reported that 6.4% (8/125) of the adverse events seen were considered to be related to treatment with vonicog alfa. Two of these were reported to be serious: chest discomfort and increased heart rate in 1 participant. Peyvandi et al. (2018) reported 12 treatment-emergent adverse events in 6 participants. Two of these participants each had 1 serious adverse event: diverticulitis (a digestive condition) that was not thought to be treatment related and DVT that was considered to be possibly related to vonicog alfa treatment. One participant had a positive result for anti-von Willebrand factor binding antibodies (which were reported to be non-inhibitory), but no adverse events were reported for this participant.

There were no other findings of thromboembolic events, anti-von Willebrand factor neutralising or binding antibodies, factor 8 neutralising antibodies, or antibodies against rFurin, Chinese hamster ovary host cell proteins, or murine immunoglobulin G.

Evidence gaps and limitations

The main limitations of the studies included their small size (n=22 for efficacy analysis and n=37 for safety analysis in Gill et al. 2015 and n=15 in Peyvandi et al. 2018), the design of the study (open-label and non-comparative), co-administration with other treatments (such as recombinant factor 8) and subjective outcome measures. However, these limitations are as expected and considered acceptable for studies investigating treatment in people with bleeding conditions given that: the indications of interest were episodic and recruitment was limited to severe types of VWD; it would be impractical and unethical to blind participants who are bleeding and treat them with placebo; in practice the most commonly used plasma-derived concentrates already contain both factor 8 and VWF; and subjective assessments are commonly used for assessing treatment efficacy in this population.

Both studies included people with severe VWD, across all types who previously needed plasma-derived VWF, and most (but not all) of these were people with type 3 VWD. These patients fit the licensed indications. There were no quality of life outcomes reported in the studies.

8 Proposed Criteria for Commissioning

Patient eligibility criteria

Vonicog alfa will be routinely commissioned 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); AND
- when VWF activity levels are <50 IU/dl (see British Society of Haematology guidelines on the diagnosis and management of von Willebrand disease 2014) OR diagnosis is type 2N VWD; AND
- there is no evidence of inhibitors to VWF.

Retreatment for the same bleeding episode or surgery should be guided by clinical presentation, taking into account the half-life of vonicog alfa, with careful monitoring of the necessary laboratory parameters and the patient.

Patients, or their carers, should be encouraged to provide their clinical team with information on treatments received for the previous bleeding episode or surgery and related clinical sequelae. This is most easily achieved through the use of a secure therapy recording digital interface.

Stopping criteria

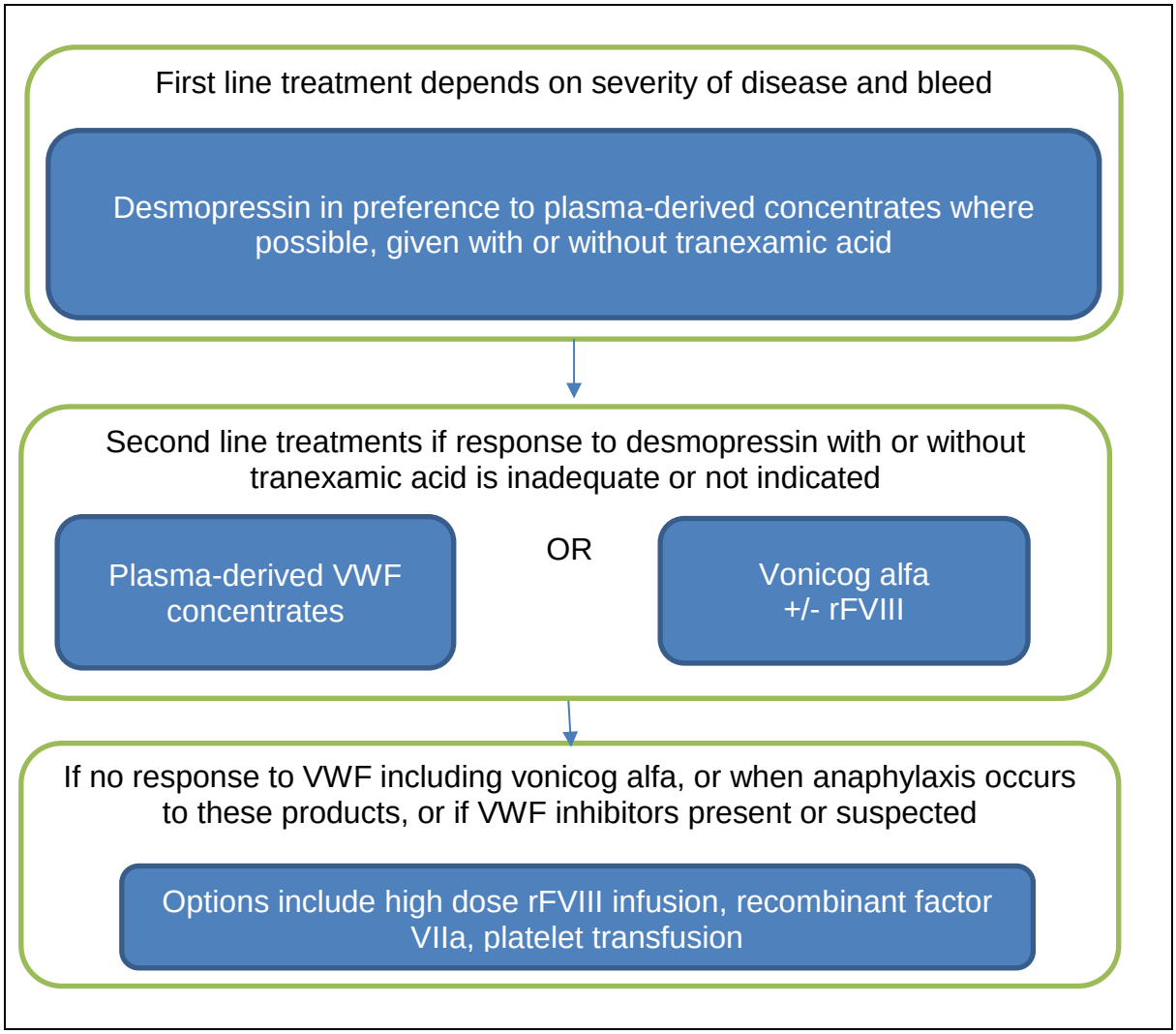
Treatment with vonicog alfa should be monitored and compared to the effectiveness with previous treatment episodes. Treatment should be discontinued if the following occur:

- reduced or poor control of bleeding with vonicog alfa compared with previous treatment episodes
- unexpected bleeding despite maintenance of therapeutic levels of VWF activity (50 IU/dl or more)
- emergence of adverse effects considered linked to vonicog alfa, such as DVT, hypersensitivity, and infusion-related reactions
- development of anti-VWF neutralising or binding antibodies

9 Proposed Patient Pathway

The choice of treatment for treating bleeding episodes, and treating and preventing bleeding during surgery, will be based on the efficacy of the product to control the severity of bleed, and the type and location of surgery, taking into account clinical evaluation and shared decision making with the patient where appropriate. The pathway below outlines that vonicog alfa will be available as a second line treatment, given when desmopressin and tranexamic acid treatment are ineffective or not indicated.

Plasma derived VWF is current standard of care at second line, and it will remain a treatment choice at this point in the pathway. Historically in the UK, recombinant factor concentrates (when available) have been used in preference to plasma derived products on account of historical problems with transfusion transmitted infection (as noted by Gill et al. 2015). Although the safety record of modern plasma derived factor concentrates is excellent, it is anticipated that the principle of 'recombinant for all' will be an important consideration in choice of product. There is currently no evidence from clinical studies that vonicog alfa has any other advantage over plasma derived VWF concentrate. When more than one product is deemed suitable, the product with the lowest overall acquisition cost to control a bleed should be chosen (taking into account the cost of co-administration with recombinant factor 8 [rFVIII] where required).



10 Proposed Governance Arrangements

Vonicog alfa will only be commissioned for adults with VWD at providers with an NHS England contract and which are compliant with the service specification for haemophilia (B05/S/a 2013/14 NHS standard contract for haemophilia [all ages]).

Treatment with vonicog alfa should be under the supervision of a physician experienced in the treatment of haemostatic disorders.

11 Proposed Mechanism for Funding

The proposed mechanism for funding is via established mechanisms for high-cost tariff-exempt drugs to NHS England Specialised Commissioning teams.

12 Proposed Audit Requirements

Specialised centres will be required to ensure that processes are in place to track decisions to treat and evidence of effectiveness. Patients with VWD should be registered in the National Haemophilia Database (NHD) and any products used to manage bleeding episodes in VWD should be recorded within the NHD. Centres may use software systems to track and audit use of vonicog alfa, in order to ensure it is administered according to the Criteria for Commissioning.

13 Documents That Have Informed This Policy Proposition

The documents that have informed this policy proposition include a review of the clinical evidence available for vonicog alfa, the European public assessment report (EPAR), Summary of product characteristics (SPC), as well as the publications listed in the reference section below.

14 Date of Review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or not for-routine commissioning.

15 References

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