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CADTH COMMON DRUG REVIEW

Patient Input

von Willebrand Factor [recombinant] (Vonvendi)

(Shire Pharma Canada ULC, now part of Takeda)

Indication: von Willebrand disease, adults, treatment and perioperative management

CADTH received patient input from:
Canadian Hemophilia Society

February 21, 2020

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Patient Input Template for CADTH CDR and pCODR Programs

Name of the Drug and Indication	Vonvendi, indicated for the treatment and control of bleeding and in perioperative management in patients aged 18 years and older with von Willebrand disease.
Name of the Patient Group	Canadian Hemophilia Society
Author of the Submission	David Page, with input from members of the CHS Blood Safety and Supply Committee
Name of the Primary Contact for This Submission	[redacted]
Email	[redacted]
Telephone Number	[redacted]

1. About Your Patient Group

If you have not yet registered with CADTH, describe the purpose of your organization. Include a link to your website.

Founded in 1953, the Canadian Hemophilia Society (CHS) is a national voluntary health charity. Its mission is to improve the health and quality of life of all people in Canada with inherited bleeding disorders and ultimately find cures. Its vision is a world free from the pain and suffering of inherited bleeding disorders.

The Canadian Hemophilia Society (CHS), whose national headquarters are in Montreal, is an organization that works at three levels: nationally, provincially and locally. We have ten provincial chapters across the country.

Its Board of Directors is made up of 16 individuals with valuable skills and representing the organization's 10 provincial chapters. Each provincial chapter in turn is managed by its own Board of Directors. Many chapters are separately incorporated and have their own charitable registrations. Three provinces—Quebec, Ontario and Manitoba—currently have offices with permanent staff. The national organization and its chapters share a common vision and mission. The CHS has approximately 300 active volunteers across the country, including people affected by bleeding disorders, family members and health care providers who work in the bleeding disorder treatment centres.

The CHS is affiliated with the World Federation of Hemophilia (WFH) and its more than 125 National Member Organizations around the world; the WFH is officially recognized by the World Health Organization. We work in collaboration with the health care providers in Canada's 26 inherited bleeding disorder treatment centres, the blood system operators (Canadian Blood

Services and Héma-Québec), the Network of Rare Blood Disorder Organizations and the Canadian Organization for Rare Diseases, and others who share our common interests.

The CHS receives funding from a number of pharmaceutical companies that are present in the Canadian market for coagulation therapies. These include Bayer, Sanofi, CSL Behring, Novo Nordisk, Octaphama, Pfizer, Roche and Tekada. None of these companies was involved in the preparation of this submission nor did any contribute funding to support it.

Charitable Registration: 11883 3094 RR 0001

Website: hemophilia.ca

2. Information Gathering

CADTH is interested in hearing from a wide range of patients and caregivers in this patient input submission. Describe how you gathered the perspectives: for example, by interviews, focus groups, or survey; personal experience; or a combination of these. Where possible, include **when** the data were gathered; if data were gathered **in Canada** or elsewhere; demographics of the respondents; and **how many** patients, caregivers, and individuals with experience with the drug in review contributed insights. We will use this background to better understand the context of the perspectives shared.

There are 4,321 people (1,542 males and 2,776 females) identified with VWD in Canada (source: data supplied to the 2018 World Federation of Hemophilia Global Survey from the Canadian Bleeding Disorder Registry and BC's ICHIP registry). Only 96 of these people have been diagnosed with Type 3 VWD, the most severe form, who sometimes require prophylactic (preventive) therapy. While these numbers are considered to be accurate regarding those treated in the Canadian network of 26 Canadian bleeding disorder treatment centres, it is well-known that VWD, especially in its milder forms, is significantly under-diagnosed.

People with VWD have been members of CHS and its chapters for decades and serve on our national and chapter Boards of Directors.

The CHS has gathered information on the VWD patient perspective in a number of ways.

CHS is in regular contact with its members through chapter meetings where current and future therapies are often discussed. Every year, CHS, in collaboration with the physicians, nurses and other health care providers who work in Canadian bleeding disorder treatment centres, organizes a national medical/scientific symposium that features the latest in bleeding disorder research. In 2018, this symposium was dedicated entirely to issues of relevance to women with bleeding disorders, notably von Willebrand disease. The 2019 symposium, held May 24, entitled "The Dawn of a New Era" was devoted to the evolution of therapies for bleeding disorders, including von Willebrand disease.

To collect specific perspectives from patients and caregivers with VWD on the burden of disease and treatment, satisfaction with current treatment and the improvements people would like to see in a new treatment, the CHS conducted an on-line survey between January 15 and January 31, 2020. The survey was publicized via different CHS and chapter communication tools, including the CHS website, email, Facebook and Twitter. We received 7 responses from 4 provinces. All respondents are affected by VWD. The results of that survey are presented in the following pages.

In addition, CHS consulted leading physician opinion leaders in the treatment of VWD.

3. Disease Experience

CADTH involves clinical experts in every review to explain disease progression and treatment goals. Here we are interested in understanding the illness from a patient's perspective. Describe how the disease impacts patients' and caregivers' day-to-day life and quality of life. Are there any aspects of the illness that are more important to control than others?

Respondents said that VWD …

- has been a huge negative factor in life, affecting everything.
- has proven very disabling.
- has caused swelling from stressed limbs, muscles, ligaments, joints which is difficult to manage.
- has caused pain.
- causes frequent nosebleeds, bruises and joint bleeds. The joint pain and menstrual issues have increased with age.
- has meant long, heavy menstruations.

The impact of VWD on quality of life is borne out by research. Multiple studies have found that 74-100% of women with VWD suffered from heavy menstrual bleeding, a rate much higher than any other bleeding disorder including hemophilia A and B. Post-partum bleeding affects 20% of women. (MacKensen. Haem 2011;17 (sup 1):33-37 James. Haem 2005;11:295. Lopez.Blood 1998;91:4397. El-Hemaidi. Curr Op Obst Gyn 2007;19(6):513-20. Demers. Int J Gyn Obst 2006;95(1):75-87. Hacioglu. J Obst Gyn 2016;36 980:1041-45.) VWD affects people's ability to work; 38-47% of women with bleeding disorders, in majority VWD, had significant loss of time from work or school (Kadir. Haemophilia 1998;4:836-41. Kouides. Haemophilia 2000;6:643-8. Kadir. Haem 2010;16:832-9. Hacioglu. J Obst Gyn 2016;36 (8):1041-45. Rae. Haem 2013;19:385-91.)

4. Experiences With Currently Available Treatments

CADTH examines the clinical benefit and cost-effectiveness of new drugs compared with currently available treatments. We can use this information to evaluate how well the drug under review might address gaps if current therapies fall short for patients and caregivers.

Describe how well patients and caregivers are managing their illnesses with currently available treatments (please specify treatments). Consider benefits seen, and side effects experienced and their management. Also consider any difficulties accessing treatment (cost, travel to clinic, time off work) and receiving treatment (swallowing pills, infusion lines).

Respondents said:

- It stops my bleeding.
- It temporarily stopping the bleeds.
- OK.
- A better treatment system would be great.
- Good.
- I think it's managed at a satisfactory level. I am always willing to try something better or more effective.

- Bonne.
- I take Humate P and it works awesome but when I'm bleeding I can't get to hospital to get it.
- I need treatment with Humate P when needed. The cost for travel to hospital is increasing.
- I infuse 2 to 3 times per week.
- I have to take time off school. I have side effects, flu-like symptoms.
- I manage with rest, anti-inflammation creams, icing, and elevation.
- I am currently using Humate P. There are some mild side effects: prickly feeling, headaches, fatigue after infusions. I have no difficulty accessing treatment or supplies. I've been on Humate P only. Younger, I used fresh frozen plasma.
- Cyklokapron : facilement accessible mais cause de la diarhée. DDAVP en sous-cutané: facile à faire mais pas disponible partout.

The complaints mentioned here would not be ameliorated by Vonvendi in comparison to other clotting factor concentrates currently available to treat VWD (Humate P, Wilate) as the efficacy, half-life and treatment schedules are similar. Safety, however, may in some situations be improved. See section 5.

5. Improved Outcomes

CADTH is interested in patients' views on what outcomes we should consider when evaluating new therapies. What improvements would patients and caregivers like to see in a new treatment that is not achieved in currently available treatments? How might daily life and quality of life for patients, caregivers, and families be different if the new treatment provided those desired improvements? What trade-offs do patients, families, and caregivers consider when choosing therapy?

Respondents said:

- Easier to get treatments and closer to home.
- Less burdensome treatment and longer lasting for better quality of life.
- Just worried about lifestyle in the future.
- Daily dose of something majorly anti-inflammatory would help significantly, allowing less missed days from work.
- Less side effects.
- A longer half-life, less side effects and easier administration would be ideal. While self-infusion is usually easy for me, some days are hard.
- Ne pas avoir à prendre des comprimés en plus d'une injection.

CHS comments:

There are many types of VWD: type 1, type 2A, type 2B, type 2N, type 2M and type 3. They have different severities and require different treatments, including hormone therapy, desmopressin, antifibrinolytics, and factor replacement (plasma-derived VWF-FVIII), sometimes in combination. There is no doubt that quality of life is significantly reduced for many with VWD. While treatment can be burdensome, notably IV infusion, and is associated with some side effects, the patients surveyed reported that their current treatments are fairly effective in stopping and preventing bleeding.

Recombinant Vonvendi® is the first "pure" von Willebrand factor (VWF); that is, it contains no factor VIII (FVIII). Other VWF concentrates available in Canada all contain FVIII in varying ratios. Thus, Vonvendi confers an advantage in situations where the additional FVIII is not needed or is even contraindicated. Two such situations are:

1. When the risk of bleeding is high enough (e.g. Type 3 VWD) that regular preventive replacement therapy with VWF is required (prophylaxis). Exogenous FVIII is not required in this setting, even for patients with very low baseline FVIII, as the normal VWF will pick up endogenous FVIII and increase its half-life 6 - 12 hours after the first infusion.
2. In surgical situations, including post-caesarean, and post-partum, where large doses of VWF-FVIII are infused over several days or weeks. With current VWF-FVIII concentrates, FVIII accumulates over time, increasing the risk of thrombosis. A pure VWF concentrate like Vonvendi would reduce the risk in such situations.

In addition, because of past contamination of clotting factor concentrates with HIV and HCV, there are patients who will refuse plasma-derived VWF-FVIII because of perceived risk but who would accept a recombinant VWF preparation such as Vonvendi if it were available.

6. Experience With Drug Under Review

CADTH will carefully review the relevant scientific literature and clinical studies. We would like to hear from patients about their individual experiences with the new drug. This can help reviewers better understand how the drug under review meets the needs and preferences of patients, caregivers, and families.

To our knowledge, there is no clinical trial experience with Vonvendi in Canada.

7. Companion Diagnostic Test

If the drug in review has a companion diagnostic, please comment. Companion diagnostics are laboratory tests that provide information essential for the safe and effective use of particular therapeutic drugs. They work by detecting specific biomarkers that predict more favourable responses to certain drugs. In practice, companion diagnostics can identify patients who are likely to benefit or experience harms from particular therapies, or monitor clinical responses to optimally guide treatment adjustments.

What are patient and caregiver experiences with the biomarker testing (companion diagnostic) associated with regarding the drug under review?

Consider:

- Access to testing: for example, proximity to testing facility, availability of appointment.
- Testing: for example, how was the test done? Did testing delay the treatment from beginning? Were there any adverse effects associated with testing?
- Cost of testing: Who paid for testing? If the cost was out of pocket, what was the impact of having to pay? Were there travel costs involved?
- How patients and caregivers feel about testing: for example, understanding why the test happened, coping with anxiety while waiting for the test result, uncertainty about making a decision given the test result.

No comment.

8. Anything Else?

Is there anything else specifically related to this drug review that CADTH reviewers or the expert committee should know?

CHS takes the position that Vonvendi has value, especially to avoid potential serious thrombotic side effects, in specific clinical situations.

If approved for reimbursement, CHS strongly recommends that it be distributed by Canadian Blood Services, similarly to other VWF concentrates currently available.

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Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

No.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

No.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Tekada				X
CSL Behring			X	
Octapharma			X	

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: David Page
Position: National Director of Health Policy
Patient Group: Canadian Hemophilia Society
Date: February 21, 2020