CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

efanesoctocog alfa (TBC)

(Sanofi-aventis Canada Inc.)

Indication: Efanesoctocog alfa is a long-acting recombinant antihemophilic factor (coagulation FVIII) with high sustained FVIII activity indicated in adults and children with hemophilia A (congenital FVIII deficiency) for: • Routine prophylaxis to reduce the frequency of bleeding episodes • On-demand treatment and control of bleeding episodes • Perioperative management of bleeding

September 27, 2024

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CADTH in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings.

Disclaimer: The views expressed in this submission are those of the submitting organization or individual. As such, they are independent of CADTH and do not necessarily represent or reflect the views of CADTH. No endorsement by CADTH is intended or should be inferred.

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CADTH does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no identifying personal information or personal health information is included in the submission. The name of the submitting group and all conflicts of interest information from individuals who contributed to the content are included in the posted submission.

Patient Group Input

No patient group input was received by the deadline of the call for input.

Clinician Group Input

CADTH Project Number: ST0840-000

Generic Drug Name (Brand Name): Efanesoctocog alfa

Indication: For use in adults and children with hemophilia A (congenital factor VIII deficiency) for routine prophylaxis to reduce the frequency of bleeding episodes, on-demand treatment and control of bleeding episodes, and perioperative management of bleeding

Name of Clinician Group: The Association of Hemophilia Clinic Directors of Canada (AHCDC)

Author of Submission: The Novel Therapy Committee members, on behalf of AHCDC

1. About Your Clinician Group

The Association of Hemophilia Clinic Directors of Canada (AHCDC) is a non-profit organization of Hemophilia Clinic Directors from across Canada. The goal of the AHCDC is to ensure excellent care for persons with bleeding disorders in Canada through clinical services, research and education. Our members are involved nationally and internationally in regulatory trials and research studies that investigate new factor replacement products or regimens, inhibitor development, prophylaxis, quality of life, women with bleeding disorders, genetic and clinical aspects of von Willebrand's disease. In addition, our organization promotes clinical care through support of the National Inherited Bleeding Disorder Genotyping Lab at Queen's University. The AHCDC was incorporated in Ontario in 1994. It is currently represented by Directors of all 26 hemophilia treatment centers (HTC) in Canada, and has 71 full members. The AHCDC members care for almost all Canadian patients with a definite hemophilia diagnosis. AHCDC owns and manages the Canadian Bleeding Disorders Registry (CBDR, formerly CHARMS), a registry platform collecting demographics, clinical and quality of life data of all Canadian patients with hemophilia.

The organization's website is: www.ahcdc.ca

2. Information Gathering

The information is gathered through national advisory boards, expert opinions, and clinical trial experience from Canadian pediatric and adult HTCs who participated in the clinical trial. The document was drafted by members from the AHCDC Novel Therapy committee. It is circulated to AHCDC board for input and feedback before submitting the final version.

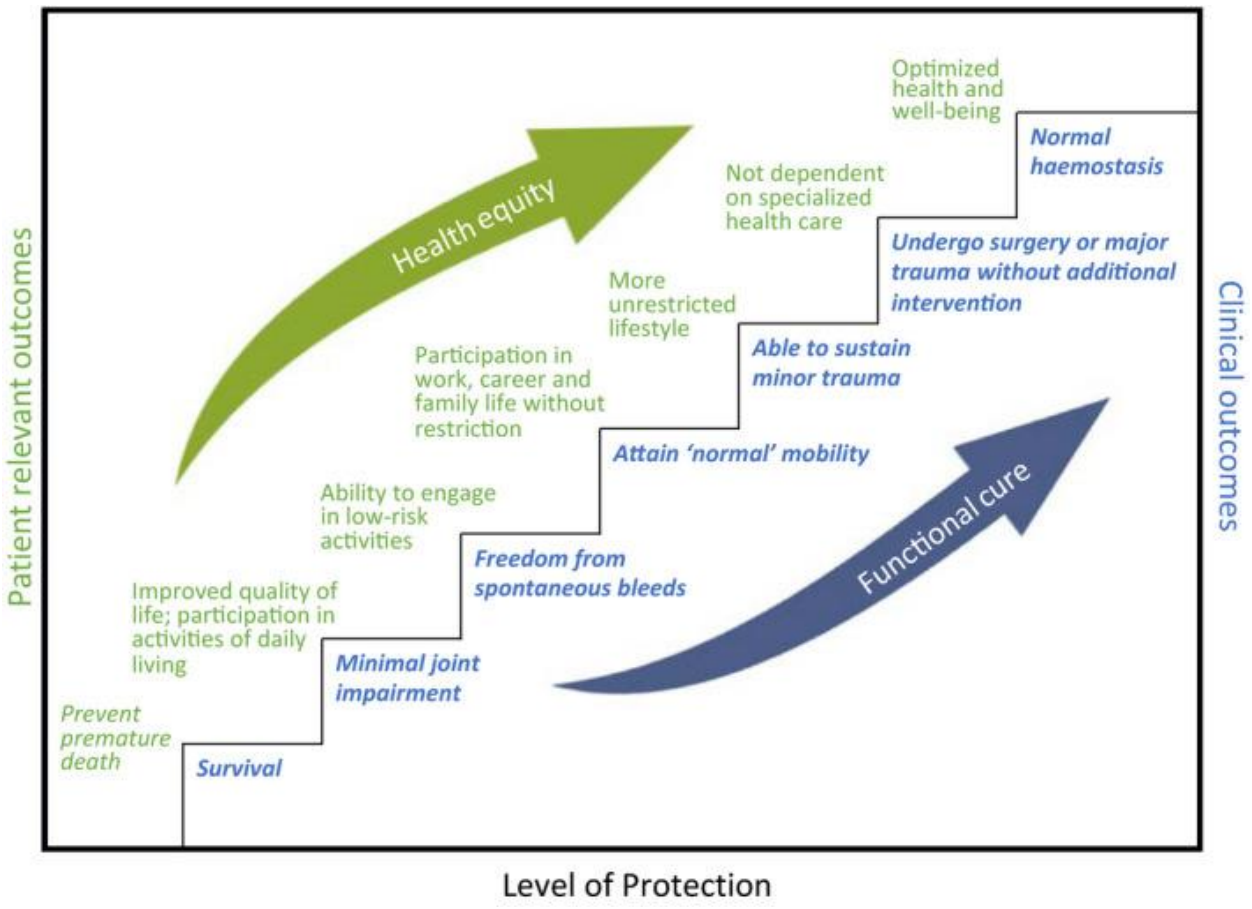
3. Current Treatments and Treatment Goals

Hemophilia A is an X-linked recessive bleeding disorder characterized by a deficiency of coagulation factor VIII (FVIII), affecting approximately 1 in 10,000 people, or about 3900 Canadians [1]. Hemophilia A is classified as mild (baseline FVIII activity 0.05-0.40 IU/ml), moderate (FVIII 0.01-

<0.05 IU/ml) and severe (FVIII <0.01 IU/ml). Persons with severe hemophilia A and a proportion of those with moderate hemophilia A suffer from frequent and severe bleeding that can lead to disability and early mortality [2]. This takes the form primarily of recurrent bleeding into joints and muscles, and life-threatening bleeds such as intracranial hemorrhage (ICH). Repeated bleeds into joints result in progressive joint damage (hemophilic arthropathy), chronic pain, loss of function, absences from school and work, impaired productivity, and the need for early orthopedic interventions such as joint arthroplasties.

The standard of care in Canada for persons with hemophilia A (PWHA) with a severe bleeding phenotype, consistent with the World Federation of Hemophilia (WFH) Guidelines for the Management of Hemophilia, entails regular prophylactic replacement therapy with clotting factor concentrates (CFCs) or non-factor subcutaneous therapy [2]. The goal of prophylaxis, the regular administration of therapeutic agents aimed at maintaining hemostasis, has evolved over the past decades. Historically, prophylaxis with FVIII replacement targeted a trough FVIII activity of 0.01 IU/ml (1%) or higher (i.e. in the moderate hemophilia range), with the goal of preventing spontaneous bleeding into joints and muscles, life-threatening bleeds such as ICH, and the progression of joint damage. This was based on the observation that persons with moderate hemophilia have a lower risk of bleeding than those with severe hemophilia and a lower prevalence of arthropathy and other bleed-related morbidities. However, growing evidence over the years demonstrated that despite prophylaxis, PWHA still experience life-threatening bleeds, joint bleeds, and hemophilic arthropathy, leading the WFH to acknowledge that a FVIII trough of 0.03-0.05 IU/ml (3-5%) or even higher may be required to prevent bleeds [2-4]. Furthermore, the lives of PWHA were often restricted by avoidance of any moderate to intense physical activities, prohibition of sports associated with high risk of life or limb-threatening bleeds, and restriction of employment opportunities. Consequently, there has been a **paradigm shift, moving away from preventing early death and reducing spontaneous bleeds or from targeting a specific FVIII trough level**, **towards achieving health equity** [5]. A recent patient and clinician panel from over 20 countries developed a 7-level treatment model to achieve functional cure and health equity for PWHA [5] (Figure 1). This is echoed by the WFH guidelines, highlighting the goal to empower PWHA to lead healthy and active lives, and to participate fully in physical and social activities similar to the general population [2]. The current standard of care in Canada includes individualized or personalized prophylaxis, based on patient- and disease-related factors such as bleeding rates, joint health, physical activity and occupation, FVIII CFC pharmacokinetics calculated from population modeling, and the need for antiplatelet or anticoagulant therapy [6].

Figure 1. Model of Milestones towards normal hemostasis [5].



In Canada, FVIII CFCs and non-factor replacement therapies are provided by the Canadian Blood Services (for provinces outside of Québec) and Héma-Québec (in the province of Québec). Currently available treatment approaches for Hemophilia A are:

a) FVIII CFCs: Currently available FVIII CFCs include standard half-life (SHL) factor CFCs (Kovaltry®, Xyntha®) and extended half-life (EHL) CFCs (Adynovate®, Eloctate®, Jivi®, Esperoct®).

b) Non-factor replacement therapy: The only currently available non-factor replacement therapy for hemophilia A outside of clinical trials is emicizumab, a bispecific monoclonal antibody administered subcutaneously. Emicizumab has been available for Canadian PWHA with inhibitors, severe hemophilia A without inhibitors, and more recently expanded to mild-moderate hemophilia A who requires or would benefit from prophylaxis. In addition, there are other upcoming non-factor replacement therapies available through clinical trials, and may eventually become available in the Canadian market within the next 2-5 years. These include RNA interference therapy targeting antithrombin (fitusiran), and monoclonal antibodies against tissue factor pathway inhibitors (anti-TFPI).

c) Gene therapy: Hemophilia A gene therapy (valoctocogene roxaparvovec [Roctavian]), a one-time treatment inserting a functional FVIII gene into somatic cells, provides the possibility of sustained FVIII expression and long-term phenotypic cure for PWHA. While it has been approved by the US Food and Drug Administration and European Medicines Agency, it has yet to obtain Health Canada approval. The manufacturer announced in August that it would limit marketing of valoctocogene roxaparvovec to the U.S., Germany and Italy. Therefore, it is extremely unlikely that this gene therapy will come to Canada in the foreseeable future.

While achievement of a higher FVIII trough is critical in preventing spontaneous and traumatic bleeds, preserving long-term joint health, and enabling PWHA to participate in active healthy lives, logistically it may not be achievable for everyone. Targeting a higher FVIII trough requires frequent administration of high doses of FVIII CFCs (typically 2-3 times a week or more frequently), and may not be feasible in pediatric populations or adults with poor venous access. This is largely limited by short FVIII half-life. This limitation is only partially addressed by current EHL FVIII CFC, owing to the interaction between infused FVIII and endogenous von Willebrand factor (VWF). With the advent of emicizumab for PWHA without inhibitors, the majority of Canadian PWHA have switched from FVIII CFCs to emicizumab due to ease of administration, comparable or superior bleeding protection in most patients, long half-life, and steady state levels. However, emicizumab provides bleeding protection (thrombin generation) equivalent to a FVIII activity of 9-20% in primate and mouse models [7, 8]. While effective in preventing bleeds in routine daily activities, it does not provide peak levels like FVIII CFCs and may not offer sufficient protection for intense physical activities or occupations.

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

There are several unmet needs despite the currently available treatments in Canada for PWHA with severe bleeding phenotype. We will discuss this based on current treatments (FVIII CFCs and emicizumab).

<u>Unmet needs of PWHA on prophylaxis with SHL or EHL FVIII CFCs</u>

Prophylactic FVIII CFC replacement requires frequent venipuncture by patients and/or caregivers long-term, typically 2-3 intravenous infusions per week. Even with the advent of personalized regimens based on pharmacokinetics (PK) and the use of EHL FVIII CFCs, many PWHA still need to self-infuse frequently to maintain a higher FVIII trough needed to minimize bleeds and enable participation in sports and physical activities. Many individuals have poor venous access, posing a major challenge to routine prophylaxis. While placement of a central venous catheter (generally a Port-a-catheter) is an option, it is associated with long-term complications including risks of infection, bleeding, thromboembolism, and loss of function requiring removal. Even among PWHA

with adequate venous access, non-adherence and/or treatment burden pose as key barriers to effective prophylaxis.

Second, the efficacy of prophylaxis with existing SHL and EHL FVIII CFCs is variable. Even with the routine adoption of individualized, PK-guided prophylaxis in Canada, many PWHA are still unable to achieve the goal of zero bleeds. Breakthrough bleeds and long-term joint damage predispose patients to a life of pain, loss of function, school/work absenteeism and disability. A modified Delphi consensus statement identified a target FVIII activity of 1-3% for most individuals on prophylaxis and those with mild bleeding phenotype, 3-5% for those with target joints, and up to 5-15% for those with severe comorbidities and those who experience persistent bleeds despite prophylaxis at a lower FVIII threshold (Figure 2) [6, 9]. **A growing number of studies support the rationale for targeting a higher FVIII activity as outlined in Figure 3, as FVIII activities between 15-50% have been associated with near-zero joint bleed rate in hemophilia A across a multitude of modelling studies** [9-14]. For instance, a phase 3 prospective, randomized study (PROPEL) evaluating the efficacy of PK-guided prophylaxis with two target FVIII trough levels showed a marked improvement in the achievement of zero bleeds in the higher trough group (FVIII 8-12%) compared with lower trough of 1-3% (67% vs 40%) [14]. However, 72% of participants had to infuse EHL FVIII CFCs daily or every other day to achieve the higher trough level, imposing substantial treatment and financial burden [14]. The intense infusion frequency demonstrated in the PROPEL trial is not feasible in a real-world setting for most PWHA.

Figure 2. Delphi consensus on target FVIII activities for different activities and clinical scenarios [6, 9].

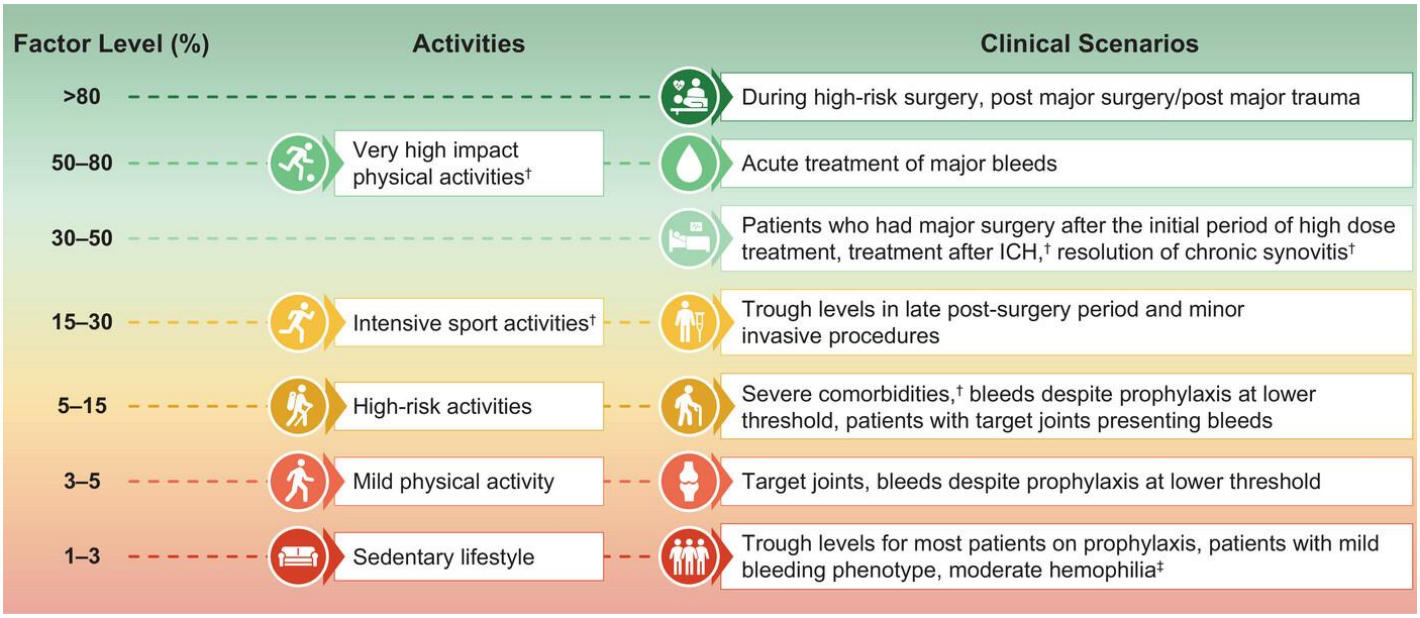
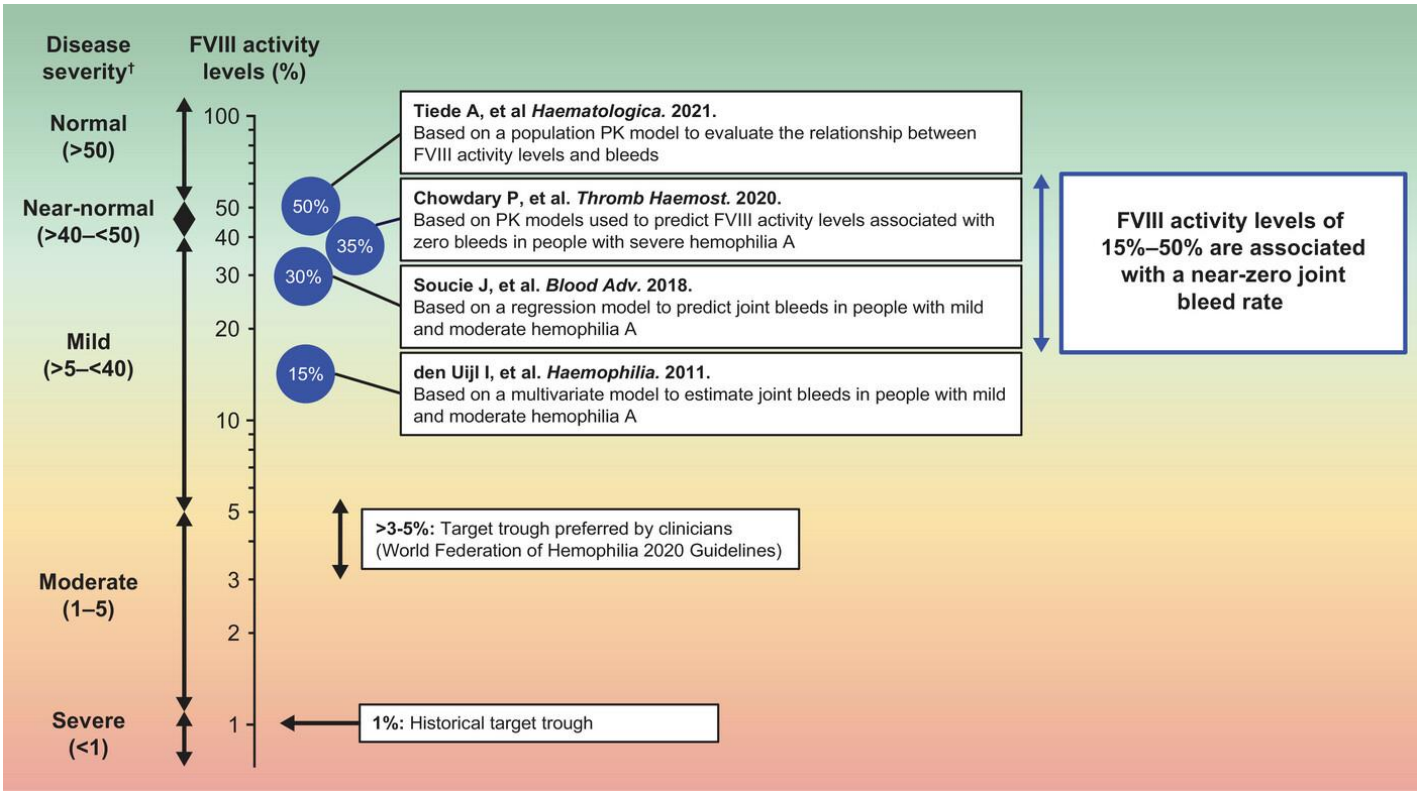


Figure 3. FVIII activities associated with near-zero joint bleeds [9].



Third, **current treatments are unable to achieve normalization/ near-normalization of FVIII activities for a meaningful, sustained duration**. Rapid decline of FVIII activities following each factor concentrate infusion cause many PWHA to live a restricted life, modifying their physical and social activities due to fear of bleeding (Table 1). The impact on quality of life and participation varies among individuals, and may include (but not limited to): inability to pursue certain occupations, inability to participate in certain sports or physical activities, fear of bleeding or pain with sexual activities, mental health problems related to treatment burden, and chronic pain. The impact of hemophilia on quality of life has been highlighted in a number of studies [15-17]. Target FVIII activities for different physical activities have been elicited from structured expert opinions and modified Delphi method, ranging from 3-5% (mild physical activity) to 15-30% (intensive sports activities) [6]. Another expert elicitation exercise suggested minimum FVIII activities of 4-7% for low-risk activities (in people without and with joint disease) and 38-47% for high-risk activities (in people without and with joint disease) [18].

Fourth, FVIII trough levels associated with FVIII CFC or emicizumab prophylaxis are often insufficient to allow for safe anticoagulation or dual antiplatelet therapy. Historically, PWHA have a shorter life expectancy than the general population due to life-threatening hemorrhages, as well as blood-borne pathogens such as human immunodeficiency virus and hepatitis C from tainted blood products. As the life expectancy of PWHA is approaching that of the general population, we

observe a rise in the prevalence of cardiovascular and cerebrovascular diseases requiring antiplatelet or anticoagulation therapy. This provides a clinical conundrum, and is challenging to manage even with the use of aggressive prophylactic therapy.

Table 1. Comparison of half-lives of current EHL-FVIII therapies, subject to VWF-imposed half-life ceiling from binding of FVIII CFCs and endogenous VWF.

Technology for FVIII half-life extension	**EHL $t_{1/2}$**	**Standard rFVIII comparator $t_{1/2}$**	**Half-life extension ratio[23,a]**
Fc fusion[19]	19.0 h	12.4 h	1.5
Glyco-PEGylation[20]	18.4 h[b]	11.7 h[b,c]	1.6
Cys variant-PEGylation[21]	18.4 h	13.0 h	1.4
Amino group-PEGylation[22]	14.3 h	10.4 h	1.4

[a] Half-life extension ratio (expressed as arithmetic or geometric mean) of EHL (study rFVIII) vs rFVIII comparator for the included studies.

[b] Half-life was compared between the participant's prior FVIII treatment and N8-GP, normalized to a dose of 50 IU/kg.

[c] Multiple prior standard rFVIII products were used as comparators in the study.

Unmet needs of PWHA on prophylaxis with emicizumab

Emicizumab is effective for routine prophylaxis to reduce the frequency of bleeding events in adult and pediatric PWHA, with and without inhibitors. While it is estimated to have a FVIII equivalence of approximately 9-20%, there is inter-individual variability in emicizumab plasma concentrations. Some PWHA experience breakthrough bleeds after switching to emicizumab (due to variability in plasma concentrations or more rarely anti-drug antibodies), and may elect to switch back to prophylaxis with FVIII CFCs. Data from the Canadian Bleeding Disorders Registry showed that 73% of PWHA on emicizumab had zero recorded bleeds over a median follow-up of 249 days [24]. Of the 145 individuals on emicizumab with recorded bleeds, 13% had spontaneous bleeds [24]. Due to

its steady-state level without a peak effect, it may not provide adequate hemostatic protection for high-risk sports and physical activities (Figure 2).

There is also a growing cohort of elderly PWHA who are accruing risk factors for cardiovascular disorders and thromboembolic events necessitating initiation or intensification of FVIII CFC therapy to allow antithrombotic therapy.

Overall, there is a pressing need to provide effective therapy for a subgroup of PWHA with a severe bleeding phenotype, who continue to experience breakthrough bleeds despite routine prophylaxis with emicizumab or with SHL/EHL FVIII CFCs, and those who are not good candidates for emicizumab due to the need for a higher FVIII equivalent. The ultimate goal, in keeping with the WFH treatment guidelines, is to minimize the number of bleeds to zero or near-zero, slow down the progression of hemophilic arthropathy, and minimize the adverse impact of recurrent bleeds on physical activity, physical and social function, and productivity loss. Prophylaxis with efanesoctocog alfa once weekly provides FVIII activity within or near the normal range with infrequent intravenous infusion, superior bleeding protection, and improvement in pain and joint health, especially for the subset of PWHA who are not optimally controlled on existing prophylactic therapeutic options.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

The availability of emicizumab has been truly paradigm changing for most people with severe hemophilia A. Approximately 75% of Canadians with severe hemophilia A have switched from FVIII to emicizumab prophylaxis, resulting in reduced treatment burden, improved satisfaction, and excellent bleed protection in the majority. In addition, a growing number of Canadians with moderate hemophilia A have switched or are in the process of being switched from FVIII to emicizumab prophylaxis, given the recently expanded access to persons with moderate hemophilia A who meet the criteria. We do not anticipate a large number of PWHA who are already doing well on emicizumab to switch back to FVIII CFC prophylaxis with efanesoctocog alfa, even with the potential benefits of normalization or near-normalization of FVIII for most of the dosing interval. However, there is a small subset of PWHA who have demonstrated intolerance or inadequate bleeding control on emicizumab, who would benefit from switching back to FVIII CFC prophylaxis. In addition, children who increase the intensity of physical activity/sports participation develop a need for higher hemostatic protection that is often unattainable with emicizumab or existing FVIII CFCs.

The remaining 20-25% of Canadians with severe hemophilia A are still using FVIII CFC for prophylaxis (mostly EHL products). Those with breakthrough bleeds despite prophylaxis would derive the most benefit from switching to Efanesoctocog alfa. This includes PWHA who engage in intense physical activity level, have advanced arthropathy, short FVIII half-life as demonstrated by PK study, poor venous access, or limited adherence to their infusion regimens. The switch would

help achieve improved bleeding protection (FVIII >40% for 4 days, maintained above 10-15% at all times with once weekly infusion), reach the goal of zero/near-zero bleeds, prevent progression of hemophilic arthropathy, and improve physical and social functioning and health-related quality of life. This is especially critical in the pediatric population with challenging venous access, in whom the once weekly regimen may obviate the need for central venous catheter insertion and related complications.

While the majority of candidates for Efanesoctocog alfa are PWHA with severe phenotype on prophylaxis, there is also a role for those with mild-moderate hemophilia A receiving on-demand or episodic therapy. Many of these patients lack venipuncture skills, requiring administration in a hospital setting at times of bleeds or surgeries. This may lead to prolonged hospital length of stay, unnecessary use of Emergency Department and hospital outpatient infusion units, and the need for visiting nurses. The ability of Efanesoctocog alfa to maintain FVIII >40% for 4 days could significantly reduce acute care utilization. Perioperative coverage may also be simplified in the general PWHA population (e.g. one single injection for many surgeries).

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Best candidates for switch to this agent:

- Pediatric population on FVIII CFCs: potential to obviate the need for central venous catheter placement
- PWHA who engage in high-risk sports or exercise programs, or are employed in occupations that put them at risk of physical injury
- Those with hemophilic arthropathy, in whom higher FVIII trough levels would minimize progression of joint damage by further reduction of bleeding risk
- Those with recurrent breakthrough bleeds despite optimization of prophylactic regimen (with either emicizumab or FVIII CFCs), who cannot tolerate emicizumab due to adverse effects, or are resistant to it due to anti-drug antibodies
- Those who need a higher FVIII trough level to facilitate antithrombotic therapy for the management of arterial or venous thromboembolic events.
- Persons with non-severe hemophilia A who require a brief period of FVIII prophylaxis (eg perioperative coverage, bleeding treatment, short period of dual antiplatelet therapy) and who do not have self-infusion skills.

PWHA who already achieve zero bleeds on prophylaxis with emicizumab or FVIII CFC and who perceive that switching to efanesoctocog alfa would have minimal impact on their quality of life, physical activity, and lifestyle are less suitable candidates.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Outcome assessment is comparable to the outcome sets used in other hemostatic (CFCs) and non-hemostatic (eg emicizumab) therapies for hemophilia. The outcomes used in clinical practice are aligned with outcomes typically used in hemophilia trials. These include:

- Annualized bleeding rates (ABR): including spontaneous, traumatic, joint, and non-joint bleeds. This is routinely collected by patients/ families on MyCBDR, and reviewed annually or more frequently by the HTC team.
- Population pharmacokinetics (PK) profile: including factor peak (recovery) and trough levels, half-life, area under the curve, amount of time FVIII activity is kept above 1%, 3%, etc. Population PK is part of standard of care used by HTC clinicians to tailor CFC prophylactic regimen (eg adjust dose, dosing frequency).
- Safety outcomes: inhibitor development, allergic or hypersensitivity reactions, thromboembolism, etc.
- Joint health: presence of target joints (a single joint with 3 or more spontaneous bleeds in a 6-month period), hemophilic arthropathy as assessed by standardized instrument such as the HJHS score and imaging. Joint health is routinely assessed during annual comprehensive hemophilia assessments by physiotherapists.
- Patient reported outcomes (PROs): some clinics use standardized instruments (e.g. PROBE) to formally measure various patient reported outcomes, others incorporate questions about PROs in routine clinic visits. Examples of PROs include health-related quality of life, physical activity, mental health, chronic pain, treatment satisfaction, treatment burden, etc.
- Healthcare resource utilization: including Emergency department visits and hospitalizations related to bleeds, outpatient unit treatments for factor infusions (e.g. for patients without venipuncture skills who require treatment for bleeds or perioperative coverage), FVIII CFC utilization, home care, etc. Factor utilization and indication (eg prophylaxis, treatment of bleed, perioperative) are routinely collected by patients/families on the MyCBDR portal, and available to HTC clinicians, and provided in aggregate form to relevant stakeholders such as Canadian Blood Services and Héma-Québec.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Consideration to discontinue treatment includes: adverse events (eg allergy, inhibitor development), decision to switch to non-factor replacement therapy, decision to undergo gene therapy or other experimental therapies, and lack of efficacy (very unlikely in this drug due to its mechanism of action).

5.5 What settings are appropriate for treatment with Efanesoctocog alfa? Is a specialist required to diagnose, treat, and monitor patients who might receive Efanesoctocog alfa?

The practice setting remains the same as other FVIII CFCs, namely under the supervision of hemophilia clinic directors within dedicated multidisciplinary HTCs. No additional special settings or specialists would be required compared to routine hemophilia care.

6. Additional Information

N/A

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

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

   AHCDC received no help from outside our clinician group to complete the submission.

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

   AHCDC received no help from outside our clinician group to collect or analyze any information used in this submission.

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. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Conflict of Interest Declaration for Organization (AHCDC)

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Pfizer				X

Takeda			X	
Novo Nordisk				X
Bayer			X	
Sanofi			X	
CSL Behring			X	
Octapharma	X			
Roche			X	

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 1

Name: Dr. Haowei (Linda) Sun

Position: Chair, Novel Therapy Committee, AHCDC; Hemophilia Clinic Director, Northern Alberta Bleeding Disorders Program; Associate Professor, Division of Hematology, Department of Medicine, University of Alberta

Date: 2024-09-03

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

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
CSL Behring	X			
Pfizer	X			
Roche	X			
Sanofi	X			
Takeda/ Shire	X			
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Dr. Jerry Teitel

Position: Past president, AHCDC; Member, AHCDC Novel Therapy Committee; Professor, Division of Hematology, Department of Medicine, University of Toronto

Date: 05-10-2023

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

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Pfizer	X			
Roche	X			
Sanofi	X			
Takeda	X			
Biomarin		X		
Vega Therapeutics		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Dr. Adrienne Lee

Position: AHCDC executive board of directors; Member, AHCDC Novel Therapy Committee

Date: 05-10-2023

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

Table 3: Conflict of Interest Declaration for Clinician 3

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Takeda	X			
Pfizer	X			
Leo Pharma	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Dr. Natasha Pardy

Position: President, AHCDC; Director, Adult Bleeding Disorders Program Newfoundland and Labrador; Clinical Assistant Professor, Discipline of Medicine, Memorial University

Date: 09-26-2024

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

Table 5: Conflict of Interest Declaration for Clinician 4

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novo Nordisk	X			
Octapharma	X			
Bayer	X			
Sanofi	X			

Roche	X			
Pfizer	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Dr. Roy Khalife

Position: Member, AHCDC Novel Therapy Committee; AHCDC executive board of directors

Date: 05-09-2024

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

Table 5: Conflict of Interest Declaration for Clinician 5

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Pfizer Canada		X		
Takeda	X			
Novo Nordisk	X			
Bayer Canada	X			
Sanofi Canada	X			
CSL Behring		X		

* Place an X in the appropriate dollar range cells for each company.

References:

1. Canadian Hemophilia Society. “Hemophilia A and B”. https://www.hemophilia.ca/hemophilia-a-and-b/

2. Srivastava A, Santagostino E, Dougall A, *et al;* WFH Guidelines for the Management of Hemophilia panelists and co-authors. WFH Guidelines for the Management of Hemophilia, 3rd edition. *Haemophilia*. 2020;26 Suppl 6:1-158.

3. Andersson NG, Auerswald G, Barnes C, *et al*. Intracranial haemorrhage in children and adolescents with severe haemophilia A or B — the impact of prophylactic treatment. *Br J Haematol* 2017;179:298-307.

4. Warren BB, Thornhill D, Stein J, *et al*. Young adult outcomes of childhood prophylaxis for severe hemophilia A: results of the Joint Outcome Continuation Study. *Blood Adv* 2020;4:2451-2459.

5. Skinner MW, Nugent D, Wilton P, *et al.* Achieving the unimaginable: health equity in haemophilia. Haemophilia. 2020; 26(1): 17-24.

6. Iorio A, Iserman E, Blanchette V, et al. Target plasma factor levels for personalized treatment in haemophilia: a Delphi consensus statement. *Haemophilia* 2017;23(3):e170-e179.

7. Lenting PJ. Laboratory monitoring of hemophilia A treatments: new challenges. *Blood Adv.* 2020; 4(9): 2111-2118.

8. Ferrière S, Peyron I, Christophe OD, et al. A hemophilia A mouse model for the in vivo assessment of emicizumab function. *Blood*. 2020; 136(6): 740-748.

9. Malec L, Matino D. Targeting higher factor VIII levels for prophylaxis in haemophilia A: a narrative review. *Haemophilia*. 2023;29(6):1419-1429.

10. den Uijl IE, Fischer K, Van Der Bom JG, *et al.* Analysis of low frequency bleeding data: the association of joint bleeds according to baseline FVIII activity levels. *Haemophilia*. 2011; 17(1): 41-44.

11. Soucie JM, Monahan PE, Kulkarni R, Konkle BA, Mazepa MA. The frequency of joint hemorrhages and procedures in nonsevere hemophilia A vs. B. *Blood Adv*. 2018; 2(16): 2136-2144.

12. Chowdary P, Fischer K, Collins PW, *et al.* Modeling to predict factor viii levels associated with zero bleeds in patients with severe hemophilia A initiated on tertiary prophylaxis. *Thromb Haemost.* 2020; 120(5): 728-736.

13. Tiede A, Abdul Karim F, Jiménez-Yuste V, *et al.* Factor VIII activity and bleeding risk during prophylaxis for severe hemophilia A: a population pharmacokinetic model. *Haematologica* 2021; 106(7): 1902-1909.

14. Klamroth R, Windyga J, Radulescu V*, et al*. Rurioctocog alfa pegol PK-guided prophylaxis in hemophilia A: results from the phase 3 PROPEL study*. Blood*. 2021; 137(13): 1818-1827.

15. Plug I, Peters M, Mauser-Bunschoten EP, *et al.* Social participation of patients with hemophilia in the Netherlands. *Blood*. 2008;111(4):1811-5.

16. Steen Carlsson K, Winding B, Astermark J, *et al*. High use of pain, depression, and anxiety drugs in hemophilia: more than 3000 people with hemophilia in an 11-year Nordic registry study. *Res Pract Thromb Haemost*. 2023;7(2):100061.

17. Nguyen NAT, Auquier P, Beltran Anzola A, *et al*; INTHEMO Study Group. Occupational integration of adults with severe haemophilia (INTHEMO): A study based on the FranceCoag registry. *Haemophilia*. 2022;28(6):962-976.

18. Martin AP, Burke T, Asghar S, Noone D, Pedra G, O'Hara J. Understanding minimum and ideal factor levels for participation in physical activities by people with haemophilia: an expert elicitation exercise. *Haemophilia*. 2020; 26(4): 711-717.

19. Mahlangu J, Powell JS, Ragni MV, *et al;* A-LONG Investigators. Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. Blood. 2014;123(3):317-25.

20. Tiede A, Brand B, Fischer R, *et al*. Enhancing the pharmacokinetic properties of recombinant factor VIII: first-in-human trial of glycoPEGylated recombinant factor VIII in patients with hemophilia A. J Thromb Haemost. 2013;11(4):670-8.

21. Coyle TE, Reding MT, Lin JC, Michaels LA, Shah A, Powell J. Phase I study of BAY 94-9027, a PEGylated B-domain-deleted recombinant factor VIII with an extended half-life, in subjects with hemophilia A. *J Thromb Haemost*. 2014;12(4):488-96.

22. Konkle BA, Stasyshyn O, Chowdary P, *et al.* Pegylated, full-length, recombinant factor VIII for prophylactic and on-demand treatment of severe hemophilia A. *Blood*. 2015;126(9):1078-85.

23. Mahlangu J, Young G, Hermans C, Blanchette V, Berntorp E, Santagostino E. Defining extended half-life rFVIII-A critical review of the evidence. Haemophilia. 2018;24(3):348-358.

24. Man-Chiu Poon, Adrienne Lee, Federico Germini, *et al;* Experience with Emicizumab Among People with Hemophilia A in the Canadian Hemophilia Bleeding Disorders Registry. *Blood* 2023; 142 (Supplement 1): 1240.

CADTH Project Number:

Generic Drug Name (Brand Name): Efanesoctocog alpha

Indication: Hemophilia A

Name of Clinician Group: CANHC (Canadian Association of Nurses in Hemophilia Care)

Author of Submission: Vanessa Bouskill, President of CANHC; Celina Woo, Incoming President of CANHC; Heather Bauman, Past President of CANHC; Lisa Thibeault, Secretary of CANHC

1. About Your Clinician Group

CANHC (Canadian Association of Nurses in Hemophilia Care) is an association of nurses across Canada who work in Hemophilia Treatment Centres (HTCs) caring for those that have bleeding disorders.

2. Information Gathering

Provided the membership of CANHC to have an opportunity to send in their comments for submission; reviewed and then collated by the executive. There are over 46 nurses in hemophilia care in 23 HTCs.

3. Current Treatments and Treatment Goals

Current treatments even new novel therapies such as Emicizumab do not completely stop bleeds from occurring. The addition of Efa (a FVIII concentrate) would allow patients improved quality of life and decrease bleeds, given the longer time that FVIIII is in the normal range (improved area under the curve). This will allow for improving QOL, decrease disease burden, reduce the severity of symptoms, minimize adverse effects, improve health-related quality of life, increase the ability to maintain employment, maintain independence, reduce burden on caregivers.

Current therapies for Hemophilia A do not offer extended half-lives like Efa, available therapies half-lives typically ranging from 12 to 19 hours, in contrast to the 48 hours provided by Efa. As a result, patients require more frequent infusions for prophylaxis, post-operative care, and injury management. The necessity for frequent infusions can lead to missed doses, negatively impacting patient adherence to treatment plans and increasing the risk of bleeding and joint health deterioration. Additionally, post-operative patients must undergo regular blood draws to monitor factor VIII levels due to the shorter half-lives associated with existing therapies, which places an extra burden on our hospital's coagulation laboratory resources and hospital bed capacity (by keeping patients in hospital longer). In contrast, the use of Efa could reduce the frequency of factor VIII monitoring and alleviate unnecessary pressure on the coagulation laboratories.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Patients are still having breakthrough bleeding with current therapies if this therapy can keep their FVIII (8) level within the normal range for 3-4 days per week this will decrease disease burden and increase QOL.

Current factor therapies present certain limitations. For instance, patients with Hemophilia may need elevated trough levels due to compromised joint health or increased levels of physical activity. Consequently, these patients may need to receive factor dosing on a daily or alternate-day basis to achieve the target factor levels necessary for preventing bleeding. Additionally, patients requiring elevated trough levels may also experience challenges with venous access due to the frequent infusions, which can lead to added stress for them or their family and potentially missed doses and poorer adherence (worst case scenario requiring central lines for venous access). Efa has the potential to maintain these same trough levels, but with just one infusion instead of requiring daily or every other day treatments with the current therapies.

Moreover, due to the nature of current therapies, patients may require daily infusions for an extended period following their procedures/surgery/major injury. Once these patients have received medical clearance, they may be discharged from the hospital with a factor treatment plan through home care nursing services. However, with the ongoing shortages in home care nursing services, arranging this care can take up to 5-7 days, necessitating that patients remain hospitalized during this period. Inadvertently increase unnecessary hospital cost. In contrast, with the extended half-life of Efa, patients may not need additional doses, and if they do, it may be limited to just one dose. Therefore, decreasing the needs from our home care nursing service partners.

Lastly, current non-Factor VIII treatments available for Hemophilia A are only administered as subcutaneous injections, and often are large volumes due to concentration of the product. This often leads to pain and difficulty with injections due to high volumes and difficulty with administering SC (especially in pediatric patients).

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

The drug under review we believe would move towards a first line treatment in combinations with other products. No other treatment would need to be tried prior to moving to Efa.

Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy? No, however, the first factor treatment to maintain a sustained factor VIII level above 40% for most of the week.

Would the drug under review be used as a first-line treatment, in combination with other treatments, or as a later (or last) line of treatment? For patients who are primarily sedentary, the use of mimetics in combination with Efa may be appropriate for surgical procedures, injuries, or high-risk physical activities. Conversely, for patients who lead a more active lifestyle or require higher trough levels due to compromised joint health, Efa should be strongly considered as the first-line treatment. Efa could also be considered for those requiring ITI to avoid central lines.

Would the drug under review be reserved for patients who are intolerant to other treatments or in whom other treatments are contraindicated? No. Efa will also be utilized for patients who engage in high-risk activities, require sustained elevated trough levels for an extended duration, experience poor venous access, or have adverse reactions to existing therapies.

Is the drug under review expected to cause a shift in the current treatment paradigm? Many patients currently utilizing factor therapies for prophylaxis have expressed a strong interest in transitioning to Efa once it becomes available. This interest is primarily due to the reduced frequency of intravenous infusions and the ability to achieve sustained Factor VIII levels exceeding 40% for most of the week.

Additionally, patients receiving Hemlibra are also considering a switch to Efa, as there are concerns about potentially losing the ability to administer intravenous treatments/or those with history of inhibitors the risk of no factor exposure and the inhibitor recurring is part of the clinical discussions.

At present, we are using Standard Half-Life (SHL) and Extended Half-Life (EHL) factor therapies for surgical interventions. It is anticipated that more clinicians may be inclined to adopt Efa due to its ability to provide sustained Factor VIII levels for a longer period, as well as the reduced need for frequent follow-up infusions and ongoing Factor VIII assay monitoring. Furthermore, we also currently utilize continuous factor infusions, which involve numerous logistical considerations that can be challenging and may lead to errors. Given the longer half-life associated with Efa, there is potential to eliminate the need for continuous factor infusions with SHLs.

Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with drug under review. Please provide a rationale for your perspective. All current therapies have a very similar half-life; therefore, Efa is the first of its kind to offer an extended half-life of 48 hours.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Which patients are most likely to respond to treatment with drug under review? All Hemophilia A severity patients for prophylaxis, injury, and/or surgeries procedures. Also, those that may require ITI therapy.

Which patients are most in need of an intervention? Patients that would benefit the most from Efa are patients that require higher factor levels due to high-risk activities, have severe joint arthropathy and/or poor venous access. Furthermore, patients undergoing surgery or procedures may also benefit from Efa, as its extended half-life provides higher factor levels for an extended period, potentially reducing the need for post-operative infusions.

How would patients best suited for treatment with drug under review be identified (e.g., clinician examination/judgement, laboratory tests (specify), diagnostic tools (specify)). We believe all patients would be suited for the treatment under review even those with mild diagnoses that require factor on demand only for trauma or procedures as often these patients do not self-infuse so the infusion burden would be decreased. Also, patients that are having breakthrough bleeds with Hemlibra and can self-infuse would benefit from switching to Efa.

Patients will be identified through a comprehensive process that includes clinical assessment and judgment, joint imaging reports, and laboratory testing.

Clinical assessment and judgement: By evaluating the patient's level of activity, we can determine if they are engaging in higher-risk activities. In these cases, Efa may be the most suitable option, as it requires less frequent infusions while maintaining sufficient factor levels throughout the week to help protect against injuries.

Joint imaging: Joints exhibiting signs of synovitis may necessitate more intensive treatment, which could involve increased factor infusions. With current factor therapies, some patients may need to infuse daily or every other day. In contrast, based on pharmacokinetic (PK) studies, Efa may only require infusions once or twice a week which is more conducive to patient adherence.

Laboratory testing: Patients may be transitioned to Efa if they demonstrate a poor half-life in relation to other factor products.

Are there any issues related to diagnosis? No

Is a companion diagnostic test required? Yes, will require Efa specific laboratory assays.

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)? No

Is it possible to identify those patients who are most likely to exhibit a response to treatment with drug under review? All patients with Hemophilia A may have varying responses to Efa, making it challenging to identify individuals who will demonstrate a more favorable response.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Are outcomes used in clinical practice aligned with the outcomes typically used in clinical trials? Yes

What would be considered a clinically meaningful response to treatment? Consider the magnitude of the response to treatment. Is this likely to vary across physicians? A clinically meaningful response to treatment would involve patients exhibiting a favorable pharmacokinetic profile, absence of bleeding events (including microbleeds/changes on imaging), and either improved or stable joint health.

Bleed rates and patients reported QOL scores are tracked/compared and discussed with every review visit. Treatment response is assessed Q1-2 years depending on severity of disease and as needed.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

The following factors would be considered: disease progression, inhibitor development, serious adverse reactions (anaphylaxis), poor half-life, poor adherence, and/or the hospital coagulation lab is unable to perform the required clotting assay for Efa.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

A bleeding disorder specialist should be the primary professional responsible for diagnosing, treating, and monitoring patients on Efa. The initial switch should be reviewed by medical professionals in the HTCs. However, if Efa is included in the treatment plan for minor or major bleeding, an emergency department physician may take the necessary steps to manage the bleeding event if the patient presents to the emergency department.

6. Additional Information

No further comments to add.

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

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

   No

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

   No

6. 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. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Vanessa Bouskill

Position: NP SickKids Hospital, Toronto

Date: 12-09-2024

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

Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Celina Woo

Position: NP BC Children's Hospital

Date: 12-09-2024

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

Table 2: Conflict of Interest Declaration for Clinician 2

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Lisa Thibeault

Position: RN Kingston General Hospital

Date: 12-09-2024

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

Table 3: Conflict of Interest Declaration for Clinician 3

Company	**Check appropriate dollar range***			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Heather Bauman

Position: RN Stollery Children’s Hospital

Date: 12-09-2024

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

Table 4: Conflict of Interest Declaration for Clinician 4

Company	**Check appropriate dollar range***

	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Michelle Bech

Position: NP St Paul's Hospital

Date: 12-09-2024

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

Table 5: Conflict of Interest Declaration for Clinician 5

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Vanessa Bourck

Position: CNS Ottawa Hospital

Date: 12-09-2024

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

Table 5: Conflict of Interest Declaration for Clinician 6

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

CADTH Project Number: **ST0840-000**

Generic Drug Name (Brand Name): **Efanesoctocog alfa**

Indication: **congenital factor VIII deficiency**

Name of Clinician Group: Canadian Physiotherapists in Hemophilia Care

Author of Submission: Julia Brooks, PT

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

We are the physiotherapists across Canada who care for patients with Hemophilia at the Hemophilia Treatment Centers. We are a core member of the treatment team and are considered the musculoskeletal experts on the team. One of the major complications in Hemophilia is joint and muscle bleeding. Our role is to assess and make recommendations around the management which includes potential options for factor replacement (in conjunction with the team).

2. Information Gathering

Please describe how you gathered the information included in the submission.

Our information is from clinician experience, conferences attended and in-services.

3. Current Treatments and Treatment Goals

Please describe the current treatment paradigm for the disease.

- Focus on the Canadian context.
- Please include drug and non-drug treatments.
- Drugs without Health Canada approval for use in the management of the indication of interest may be relevant if they are routinely used in Canadian clinical practice. Treatments available through special access programs are relevant. Are such treatments supported by clinical practice guidelines?
- Do current treatments modify the underlying disease mechanism? Target symptoms?
- What are the most important goals that an ideal treatment would address?
- **Examples:** Prolong life, delay disease progression, improve lung function, prevent the need for organ transplant, prevent infection or transmission of disease, reduce loss of cognition, reduce the severity of symptoms, minimize adverse effects, improve health-related quality of life, increase the ability to maintain employment, maintain independence, reduce burden on caregivers.

Currently in the Hemophilia A treatment paradigm there are a few different options.

First- The original short acting factor VIII replacement. This is not being used as much due to the short half-life and treatment burden for families. Some of the “longer lasting” versions of these drugs are used for patients who wanted to continue with their previous treatment or as a form of treatment for breakthrough bleeding.

Second- The “long acting” factor VIII replacement products. Used for some patients as prophylaxis if they prefer to be on an IV factor product. They are not much longer than the standard half-life products but allow for a few more hours of coverage. These can still represent a significant burden of care.

Third- The monoclonal antibodies. These allow for a stable state of protection without peaks and troughs. The sub-Q delivery significantly reduces the burden of care. The lack of a high peak can be limiting in some situations such as very active people as well as post-surgical. They also can only be used as prophylaxis and not as a treatment for bleeds once they occur.

The goals of treatment are individualized depending on a wide array of variables such as bleeding history, target joints, activity, occupation, bleeding phenotype, age, venous access and many more. The ultimate universal goal is finding a treatment that works in the patient's lifestyle, that allows them to function to their fullest potential and limits or eliminates bleeding.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Please describe goals (needs) that are not being met by currently available treatments. Examples of unmet needs:

- Not all patients respond to available treatments
- Patients become refractory to current treatment options
- No treatments are available to reverse the course of disease
- No treatments are available to address key outcomes
- Treatments are needed that are better tolerated
- Treatments are needed to improve compliance
- Formulations are needed to improve convenience

Please describe limitations associated with current treatments (e.g., adverse events, administration, etc., if applicable).

The available treatments are good for many of our patients but there are still gaps in certain areas especially in people who would benefit from a high sustained peak. Some examples of these include:

Very active patients- often the peaks from the monoclonal antibodies are not high enough to prevent bleeding but the burden of IV infusions is too high. This makes it challenging to have the best of both options.

Post surgical patients who would benefit from a sustained high level and fewer pokes as they heal.

Patients who require treatment for a bleed but don't have the IV skills to poke themselves. This means the patient must come into the center multiple times a week to receive factor which is not ideal if they are supposed to be limiting movement or if they have challenges getting into the center. Having a prolonged high level would enable us to reduce the number of visits required in a week and let them adequately care for their bleeds.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Is there a mechanism of action that would complement other available treatments, and would it be added to other treatments?

Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy?

Would the drug under review be used as a first-line treatment, in combination with other treatments, or as a later (or last) line of treatment?

Would the drug under review be reserved for patients who are intolerant to other treatments or in whom other treatments are contraindicated?

Is the drug under review expected to cause a shift in the current treatment paradigm?

Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with drug under review. Please provide a rationale for your perspective.

This drug would be used as an alternative for some patients to current treatment and could be used as a first line treatment. Generally, it would be offered as a front-line treatment once the patient is at least two years of age or older. It is the first true extended half-life factor eight product which will offer enhanced protection in the scenarios above.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Which patients are most likely to respond to treatment with drug under review?

Which patients are most in need of an intervention?

Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)?

How would patients best suited for treatment with drug under review be identified (e.g., clinician examination/judgement, laboratory tests (specify), diagnostic tools (specify))

Are there any issues related to diagnosis?

Is a companion diagnostic test required?

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)?

Is it possible to identify those patients who are most likely to exhibit a response to treatment with drug under review?

Please see above. Patients who are highly active, mild hemophilia patients who have had a bleed, post surgical patients.

This product would likely not be used in patients who do not prefer IV infusions and may not be appropriate for inhibitor patients for prophylaxis.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Are outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?

What would be considered a clinically meaningful response to treatment? Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

Examples: improved survival; reduction in the frequency/severity of symptoms (provide specifics regarding changes in frequency, severity, etc.); attainment of major motor milestones; ability to perform activities of daily living; improvement of symptoms; and stabilization (no deterioration) of symptoms.

Patients are assessed regularly (every 6-12 months) for their musculoskeletal health, bleeding frequency, and for inhibitors. Patients are also assessed on a case by case basis if they feel their bleeding is not well controlled or if they have bleeding episodes.

If the patient is having frequent joint or muscle bleeds or develops an inhibitor, then we would need to re evaluate as we do for all our factor replacement products.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Examples: disease progression (specify, e.g. loss of lower limb mobility); certain adverse events occur (specify type/frequency/severity); or additional treatment becomes necessary (specify).

Uncontrolled bleeding or inhibitor development.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Examples: Community setting, hospital (outpatient clinic), specialty clinic

If a specialist is required, which specialties would be relevant?

Patients should be followed at a Hemophilia Treatment Center and this drug must be prescribed and monitored by a trained hematologist in Hemophilia Care.

6. Additional Information

Is there any additional information you feel is pertinent to this review?

No

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

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

   No

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

   No

9. 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. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Julia Brooks

Position: Hemophilia Center Physiotherapist and Past President of Canadian Physiotherapists in Hemophilia Care

Date: 18/09/2024

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

Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Roche		X (for conference)		
Pfizer		X (for conference)		
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.