

CADTH DRUG REIMBURSEMENT REVIEW

# Pharmacoeconomic Report

Emicizumab (HEMLIBRA)

Hoffman-La Roche Ltd.

Indication: Bleeding prevention, Hemophilia A

Service Line: CADTH Interim Plasma Protein Product Review

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## Abbreviations

<b>ABTR</b>	annualized treated bleed rate
<b>BDD</b>	B-domain deleted
<b>BIA</b>	budget impact analysis
<b>FVIII</b>	factor VIII
<b>ICER</b>	incremental cost-effectiveness ratio
<b>NIS</b>	non-interventional study
<b>PMPRB</b>	Patented Medicine Prices Review Board
<b>QALY</b>	quality-adjusted life-year
<b>VWF</b>	von Willebrand factor

## Executive Summary

The executive summary is comprised of 2 tables (Table 1: Background and Table 2: Economic Evaluation) and a conclusion.

**Table 1: Submitted for Review**

Item	Description
<b>Drug</b>	Emicizumab (Hemlibra), 30.0 mg/mL, 60.0 mg/0.4 mL, 105.0 mg/0.7 mL, and 150.0 mg/mL single-use vials
<b>Submitted price</b>	Emicizumab, 30.0 mg/mL, subcutaneous injection: \$3,661.52 per vial Emicizumab, 60.0 mg/0.4mL, subcutaneous injection: \$7,323.04 per vial Emicizumab, 105.0 mg/0.7 mL, subcutaneous injection: \$12,815.31 per vial Emicizumab, 150.0 mg/mL, subcutaneous injection: \$18,307.59 per vial.
<b>Indication</b>	For patients with hemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors as routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes.  There is limited clinical experience of emicizumab use in patients with mild or moderate hemophilia A.
<b>Health Canada approval status</b>	NOC
<b>Health Canada review pathway</b>	Priority review
<b>NOC date</b>	June 14, 2019
<b>Reimbursement request</b>	For patients with severe hemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors as per HAVEN 3 trial patient eligibility, including: <ul style="list-style-type: none"><li>• Patients at significant risk of increased bleeding rates due to factors that lead to poor treatment adherence or persistence, despite being candidates for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes with factor VIII</li><li>• Patients who have limited ability to receive regular IV therapy due to other underlying factors, such as venous access challenges or geographical treatment access restrictions, despite being candidates for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes with factor VIII</li></ul>
<b>Sponsor</b>	Hoffman-La Roche Ltd.
<b>Submission history</b>	Previously reviewed: Yes <sup>a</sup> Indication: Routine prophylaxis for patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors Recommendation date: August 2, 2019

CBS = Canadian Blood Services; NOC = Notice of Compliance.

Note: The full indication is for hemophilia A (congenital factor VIII deficiency) patients with or without factor VIII inhibitors as routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes. The focus of this review relates to patients with hemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors.

<sup>a</sup> The previous review was part of a different process through CBS in which CADTH reviewed only the economics.<sup>1</sup> The details of the CBS decision are available online.<sup>2</sup>

**Table 2: Summary of Economic Evaluation**

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Patients with severe hemophilia A without FVIII inhibitors who meet the HAVEN 3 clinical trial eligibility criteria
Treatment	Emicizumab (Hemlibra)
Comparators	<ul style="list-style-type: none"> <li>• Prophylaxis with FVIII recombinants</li> <li>• On-demand FVIII recombinants (i.e., episodic use of FVIII recombinants)</li> </ul>
Perspective	Canadian publicly funded health care payer
Outcome	QALYs
Time horizon	Lifetime (98 years)
Key data source	HAVEN 3 trial
Submitted results for base case	The sequential ICER for emicizumab versus on-demand FVIII was \$1,657,813 per QALY gained. FVIII prophylaxis was ruled out by the extended dominance of emicizumab and on-demand FVIII.
Key limitations	<ul style="list-style-type: none"> <li>• The model structure does not accurately capture the clinical disease pathway or the effects of treatments appropriately.</li> <li>• Comparative clinical effectiveness was informed by the HAVEN 3 trial, which recruited a more selective population than the Health Canada indication and the sponsor's reimbursement -requested population. The Health Canada indication includes patients with hemophilia A, while the submitted reimbursement request includes only patients with severe hemophilia A or patients with mild or moderate hemophilia A who meet specific eligibility criteria. The modelled population consisted of patients with severe disease only, as per HAVEN 3's eligibility criteria. While HAVEN 3 did not recruit patients under the age of 12 years, the sponsor's base case assumed that patients entered the model at 2 years of age.</li> <li>• Given that there is no direct comparative evidence to support the efficacy of emicizumab compared to FVIII prophylaxis, the clinical outcomes for FVIII were informed by an NIS preceding HAVEN 3 conducted in patients receiving FVIII prophylaxis. According to the clinical experts consulted by CADTH, the clinical estimates used in the economic model are likely generalizable, but lack precision.</li> <li>• The sponsor's calculations assumed that drugs were dispensed to the closest milligram. However, clinical experts stated that, in practice, emicizumab and FVIII are dosed and dispensed to the nearest vial size to minimize wastage. Therefore, the sponsor's approach underestimated treatment-acquisition costs for both emicizumab and the FVIII comparators.</li> <li>• The applied treatment-specific utility estimates deviate from best-practice guidelines that recommend utility weights based on health states. The sponsor's approach to derive these utility estimates further double-counted the utility decrement associated with FVIII prophylaxis, thereby favouring emicizumab.</li> <li>• Adult patients' weights were underestimated and did not align with the clinical trial evidence. Given the weight-based dosing for both emicizumab and the FVIII comparators, this would lead to an underestimation of treatment-acquisition costs.</li> </ul>
CADTH reanalysis results	<ul style="list-style-type: none"> <li>• The CADTH reanalysis included adjusting dispensing to the nearest vial size, removing treatment-specific utility estimates, and setting patients' ages and weights to align with the HAVEN 3 trial data. CADTH was unable to address limitations associated with the model structure, patient population, and noncomparative clinical estimates derived for FVIII prophylaxis.</li> <li>• In the sequential analysis, on-demand FVIII was associated with the lowest costs and fewest QALYs, followed by FVIII prophylaxis and emicizumab. The ICER for FVIII prophylaxis compared with on-demand FVIII was \$2,298,545 per additional QALY gained, while the ICER for emicizumab versus prophylactic FVIII was \$5,530,766 per QALY gained.</li> <li>• A price reduction of 89% is required for emicizumab to achieve an ICER below \$50,000 per QALY gained, assuming the acquisition price of FVIII products reflects PMPRB published values.</li> </ul>

FVIII = factor VIII; ICER = incremental cost-effectiveness ratio; NIS = non-interventional study; PMPRB = Patented Medicine Prices Review Board; QALY= quality-adjusted life-year.

## Conclusions

CADTH undertook reanalysis to address limitations in the sponsor's submission, including adjusting dispensing to the nearest vial size, removing treatment-specific utility estimates, and setting patients' starting ages and weights to better reflect the HAVEN 3 patient population. CADTH's findings remained aligned with the sponsor's: emicizumab is not a cost-effective option at a willingness-to-pay threshold of \$50,000 per quality-adjusted life-year (QALY) in patients with severe hemophilia A without inhibitors. In the CADTH base-case reanalysis, emicizumab was associated with an incremental cost-effectiveness ratio (ICER) of \$5.53 million per QALY gained compared to factor VIII (FVIII) prophylaxis. The model was highly sensitive to the price of emicizumab and its comparators. To achieve an ICER of \$50,000 per QALY, the price of emicizumab would need to be reduced by at least 89%. However, a greater price reduction may be required if the prices of FVIII products are lower than those published by the Patented Medicine Prices Review Board (PMPRB).

While the evidence for bleeding efficacy is robust for the use of emicizumab in Canadian patients not receiving treatment with prophylactic FVIII, the evidence directly comparing emicizumab to prophylactic FVIII is limited. In patients with severe hemophilia A without inhibitors, emicizumab demonstrated statistically and clinically significant improvements in bleeding outcomes (i.e., annualized bleeding ratio for treated bleeds, all bleeds, treated joint bleeds, and treated spontaneous bleeds) compared to on-demand FVIII treatment. Limited comparative evidence exists to establish the comparative effectiveness and safety of emicizumab compared to FVIII prophylaxis, although current evidence suggests that emicizumab showed a reduction in bleeding outcomes compared to no prophylaxis (non-randomized comparison).

The Health Canada indication for emicizumab includes patients with hemophilia A regardless of their disease severity, while the sponsor's submitted reimbursement request includes only severe patients and mild and moderate patients who meet specific eligibility criteria. The modelled population only investigated patients with severe hemophilia A, as per HAVEN 3's eligibility criteria. Given that the sponsor's reimbursement request does not align with the modelled population, uncertainty remains regarding the cost-effectiveness of emicizumab in both the reimbursement-requested population and the full Health Canada indication.

## Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups, registered clinicians, and drug plans that participated in the CADTH review process.

Patient input was received from the Canadian Hemophilia Society. According to this input, hemophilia A affects patients' lives negatively on physical, psychological, and financial levels. The key concerns raised by patients are breakthrough bleeds, venous access challenges, and adherence difficulties due to the complex treatment regimen. Many patients were concerned that the standard treatment for hemophilia A without inhibitors, FVIII replacement therapy, provides insufficient protection given that breakthrough bleeds still occur, leading to a risk of chronic joint damage. The most common challenge reported by patients is difficult venous access, which is particularly challenging in infants or children. A common challenge faced by patients and caregivers is the need to travel long distances to treatment centres for check-ups, treatments, or to pick up factor supplies for home use. This can make it difficult for patients to adhere to the treatment regimen and affect caregivers' employability. A separate survey of hemophilia A health care providers with patients who have been prescribed emicizumab reported dramatic improvements in their patients' health outcomes and quality of life. These health care providers stated that patients required fewer treatment administrations, experienced less joint pain and discomfort, and had fewer hospital visits and greater treatment adherence.

In Canada, access to emicizumab is currently restricted to individuals with hemophilia A with inhibitors. Approximately 15 people with hemophilia A without inhibitors were granted compassionate access starting in autumn 2019.

Several of the following concerns were addressed in the sponsor's model:

- Since the health care payer perspective was adopted in this economic submission, patient-borne costs, such as those related to travel and lost potential income, were not considered. The sponsor included a scenario analysis adopting a societal perspective that considered the costs of productivity loss.
- Patients receiving emicizumab are expected to require fewer hospitalizations than those treated with FVIII prophylaxis, according to the health care providers surveyed. These costs have been included in the model, with fewer annual days of hospitalization associated with emicizumab compared to FVIII prophylaxis. No feedback was received on how the experience of patients receiving on-demand FVIII may differ from the experiences of those receiving emicizumab.
- Difficulties with venous access for patients receiving FVIII were captured indirectly by applying a utility improvement that was associated with subcutaneous administration (0.1112).
- Health care providers noted that patients on emicizumab experienced less joint pain and discomfort compared to patients on FVIII prophylaxis. Although the economic model assumed that the same percentage of treated bleeds would be joint bleeds (73%) across treatment options, the ABTRs were lower in patients on emicizumab. Therefore, the model aligned with the clinical experts' views. The ATBRs in the economic model were informed by HAVEN 3 and non-interventional study (NIS).

## Economic Review

The current review is for emicizumab (Hemlibra) for patients with severe hemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors as routine prophylaxis.

### Economic Evaluation

#### Summary of Sponsor's Economic Evaluation

##### Overview

The sponsor submitted a cost-utility analysis comparing emicizumab to prophylaxis with factor VIII (FVIII) and on-demand (episodic) use of FVIII. In both cases, recombinant FVIII products included: Antihemophilic Factor (Recombinant) B-domain deleted (BDD), Fc Fusion Protein (Eloctate); Antihemophilic Factor (Recombinant) PEGylated (Adynovate); Antihemophilic Factor (Recombinant) (Kovaltry); Antihemophilic Factor (Recombinant) BDD simoctocog alfa (Nuwiq); and Antihemophilic Factor (Recombinant) BDD recombinant FVIII (Xyntha). The modelled patient population reflected patients recruited in the HAVEN 3 trial, although the model start age was set to 2. This did not align with the Health Canada–indicated population nor the reimbursement-requested population. The sponsor requested reimbursement of emicizumab in eligible patients with severe hemophilia A without FVIII inhibitors, as per the HAVEN 3 trial, and in patients who were candidates for routine prophylaxis if they had limited ability to receive regular IV therapy due to factors such as venous access challenges or geographical treatment access restrictions. It also included patients who were candidates for routine prophylaxis if they were at significant risk of increased bleeding rates due to factors leading to poor adherence or persistence. No scenario analyses were provided to address the populations described by the Health Canada indication or the sponsor's reimbursement request.

The dosage regimen recommended by Health Canada for emicizumab is subcutaneous administration, with a loading dose of 3.0 mg/kg for the first 4 weeks.<sup>3</sup> This is followed by a maintenance regimen that is age- and weight-specific. Adolescent and adult patients weighing more than 40 kg have the option of 1.5 mg/kg once weekly, 3.0 mg/kg every 2 weeks, or 6.0 mg/kg every 4 weeks. In pediatric patients, and in any patients weighing less than 40 kg, the recommended maintenance regimen is either 1.5 mg/kg once weekly or 3.0 mg/kg every 2 weeks.<sup>3</sup> This aligns with the dose used in the economic model, which was based on 3.0 mg/kg as a loading dose for the first 4 weeks of treatment and 1.5 mg/kg once weekly as a maintenance dose for all ages. At the sponsor's submitted price for emicizumab of \$122.05 per mg, the cost for each single-use vial was \$3,661.52 (for 30.0 mg/mL), \$7,323.04 (for 60.0 mg/ 0.4mL), \$12,815.31 (for 105.0 mg/0.7 mL), and \$18,307.59 (for 150.0 mg/mL). For an adult patient (70 kg), the sponsor estimated the first-year annual acquisition cost of emicizumab to be \$719,946; for subsequent years, \$668,685. For FVIII prophylaxis, the annual acquisition cost was calculated by weighting the annual costs for each product by their estimated market shares. This produced an estimate of \$472,731 for an adult patient. The sponsor did not factor drug wastage in emicizumab or the FVIII comparators, assuming treatment would be dispensed to the nearest milligram.

The primary clinical outcomes of interest in the model were QALYs. The economic analysis was conducted from the Canadian public payer perspective over a lifetime time horizon (98 years). Both outcomes and costs accrued beyond the first year of the model were discounted at a rate of 1.5%, as per CADTH guidelines.

### *Model Structure*

A Markov state-transition model was submitted based on 2 health states: alive with hemophilia A, and death, with the model cycle length defined as 1 year and in which half-cycle corrections were applied (Figure 1 in Appendix 3). All patients entered the alive health state without inhibitor development. Patients had the risk of dying during each model cycle, depending on their treatment and their age. Alive patients could experience bleed events. Bleed events were stratified by the number of events experienced per year (i.e., 0, 1, 2, or 3 or more bleeds). Patients were at risk of experiencing treatment-related adverse clinical events during the first year of treatment. In addition, the model assumed no patients being treated with emicizumab or with FVIII prophylaxis would require arthroplasty, while patients being treated with on-demand FVIII would require 2 arthroplasties over the course of their lifetimes.

### *Model Inputs*

Patients entered the model at the age of 2 years. Patients' weight was sourced from the UK population. Pediatric patients were assumed to weigh, on average, 12.5 kg from ages 1 to 4, 28.6 kg from ages 5 to 13, and 60.8 kg from ages 14 to 18. Adults (greater than 18 years of age) were assumed to weigh 75.2 kg on average.

ATBRs were sourced from the HAVEN 3 trial, a 24-week, phase III, randomized controlled trial that investigated adult and adolescent patients (aged greater than 12) with severe congenital hemophilia A without FVIII inhibitors.<sup>4</sup> Patients who received episodic treatment with FVIII prior to study entry were randomized in a 2:2:1 ratio to the following treatment arms: emicizumab prophylaxis at 3.0 mg/kg weekly for 4 weeks, followed by 1.5 mg/kg weekly; emicizumab prophylaxis at 3.0 mg/kg weekly for 4 weeks, followed by 3.0 mg/kg every 2 weeks; no prophylaxis (control arm). Patients who received FVIII prophylaxis prior to study entry (derived from the NIS) were enrolled in a separate, non-randomized, single arm where they received treatment with emicizumab prophylaxis at 3.0 mg/kg weekly for 4 weeks, followed by 1.5 mg/kg weekly.<sup>4</sup> Tracking of patient trajectories in terms of the number of bleeds over time was not directly modelled; rather, the reported proportions from the trial were applied to the sponsor's economic model. This meant that the proportion of patients by the number of annual bleeding events was the same across all modelled time horizons. The model further derived the overall ATBR to inform costs and utility impacts from treatment (Figure 2, Appendix 3). Rates of clinical adverse events were sourced from the HAVEN 1 trial, a phase III, randomized controlled trial that investigated adult and adolescent patients (aged greater than 12) with hemophilia A with FVIII inhibitors.<sup>5</sup> Standardized mortality ratios, from a UK study that looked at patients with hemophilia A or B between 1977 and 1998, were applied to UK life tables for the general public.<sup>6</sup> The standardized mortality ratio for mild and moderate hemophilia was applied to patients on emicizumab and FVIII prophylaxis, while the standardized mortality ratio for severe hemophilia was applied to on-demand FVIII patients.<sup>6</sup>

Health-state utilities were derived from a de novo time trade-off vignette study conducted on the Canadian general public. Baseline utility, by treatment, was derived from this study using 2 random-intercept regression models. Differences in treatment-specific utilities were due to adjustments made according to disutilities associated with the annual number of infusions and treated bleed events expected by treatment (Figure 2) and a utility increment associated with subcutaneous administration. No disutility was captured within the economic model for adverse clinical events.

Drug acquisition costs, hospitalization due to bleeding events, and costs to manage adverse events (including arthroplasty) were considered. Dosing information was obtained from the respective Canadian product monographs, with the cost of emicizumab provided by the sponsor; the unit costs for FVIII products were sourced from the PMPRB.<sup>7</sup> Vial wastage and drug administration costs were not included. Costs of arthroplasty were taken from the reported cost per surgery from the Canadian Institute for Health Information. Adverse event and hospitalization costs were obtained from the Ontario Case Costing Initiative.<sup>7</sup>

### Summary of Sponsor's Economic Evaluation Results

The sponsor's model reported the mean of their probabilistic results, more than 5,000 model iterations. The model also reported deterministic results, which found results that were similar to the probabilistic analysis.

#### *Base-Case Results*

The sponsor's base-case results are presented in Table 3. The sponsor reported that emicizumab resulted in greater QALYs than FVIII prophylaxis and on-demand treatment. According to the sponsor's base-case results, emicizumab was associated with 40.37 QALYs, while prophylaxis and on-demand treatment were associated with 33.01 QALYs and 25.39 QALYs, respectively. However, emicizumab was more costly than its comparators, with a total expected cost of \$28,750,976 compared with \$20,116,294 and \$3,907,944 for prophylaxis and on-demand FVIII, respectively. The ICER for emicizumab was \$1,657,813 compared to on-demand FVIII. FVIII prophylaxis was subject to extended dominance through on-demand FVIII and emicizumab (combinations of on-demand FVIII and emicizumab are less costly and more effective than FVIII prophylaxis). At a willingness-to-pay threshold of \$50,000 per QALY, emicizumab had a 0% probability of being the optimal therapy.

**Table 3: Summary of the Sponsor's Economic Evaluation Results**

Drug	Total costs (\$)	Total QALYs	Sequential ICER (\$/QALY)
On-demand FVIII	3,907,944	25.39	—
FVIII prophylaxis	20,116,294	33.01	Extendedly dominated
Emicizumab	28,750,976	40.37	1,657,813

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Note: Additional results from the sponsor's submitted economic evaluation base case are presented in Appendix 3 (including cost-effectiveness acceptability curves and survival curves).

Source: Adapted from the sponsor's pharmacoeconomic submission.<sup>8</sup>

#### *Sensitivity and Scenario Analysis Results*

The sponsor included a scenario analysis in which patients could develop FVIII inhibitors while undergoing treatment. Allowing patients to develop inhibitors in the model led to a sequential ICER of \$1,271,160 per QALY compared to on-demand therapy. This change was driven largely by an increase in expected costs for both comparators. Under this scenario, no patients on emicizumab are at risk of developing inhibitors, while patients receiving the comparators were at risk of developing inhibitors and incurred increased costs from immune tolerance induction and switching to bypassing-drug treatments.

### CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the economic analysis:

- **The model structure does not appropriately capture the clinical disease pathway and the effects of treatment:** An appropriate model structure for a given economic evaluation should capture all relevant and meaningful underlying clinical or biological processes.<sup>9</sup> The model submitted by the sponsor consisted primarily of 2 health states — alive and dead — and applied transition probabilities to inform the number of patients who would die during each model cycle.<sup>7</sup> Although within the alive health state, this was further stratified by ATBRs (i.e., 0, 1, 2, or 3 or more bleeds), the sponsor did not derive transition probabilities to describe how patients would move between different bleeding strata over time. Rather, a fixed proportion of patients was applied to each bleed strata at each model cycle.<sup>7</sup> This approach is inappropriate for multiple reasons. First, given that transition probabilities were not applied directly to the model, how individuals transition among different bleeding frequency health states over time was not explicitly modelled. The clinical experts consulted by CADTH noted that, in patients with greater ATBRs, they would typically intervene to further optimize their therapy, leading to an expected decline in ATBRs. Without further intervention, these patients would be expected to have an increased risk of bleed-related morbidity and mortality outcomes. Furthermore, patients with higher bleed rates are likely to have bleed-related complications and will be at greater risk of experiencing high frequencies of bleeds in the future. However, the sponsor's submitted model did not explicitly consider any of these aspects of the condition, the impact of treatment, or its associated costs or utility impacts. Secondly, the sponsor did not incorporate parameter uncertainty. Over each Monte Carlo simulation, the same proportions were applied to the model. This is not appropriate, given that these values were derived from clinical studies and the "true" values remain unknown.
  - As this issue relates to the submitted model structure, CADTH was unable to conduct a reanalysis to assess this limitation.
- **The target population of the model does not reflect the Health Canada indication under review or the sponsor's reimbursement population.** The submitted Health Canada indication is for patients with hemophilia A (congenital factor VIII deficiency) as routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes.<sup>3</sup> The sponsor has requested reimbursement in patients with severe hemophilia A (congenital factor VIII deficiency) without FVIII inhibitors, including those who are candidates for routine prophylaxis with FVIII if they are at significant risk of increased bleed rates due to factors leading to poor adherence or persistence, or have limited ability to receive regular IV therapy due to underlying factors. During the review period, the sponsor provided additional information clarifying that the reimbursement-requested indication was for patients with severe, non-inhibitor hemophilia A as well as patients with mild and moderate non-inhibitor hemophilia A who experience geographical treatment access restrictions and venous access challenges.<sup>10</sup> The target population in the model considered only patients with severe, non-inhibitor hemophilia A who met HAVEN 3's eligibility criteria, given that key model parameters were sourced from this trial. As noted in the CADTH clinical review, the inclusion criteria for patients in HAVEN 3 included previously managed by on-demand FVIII and experiencing 5 or more bleeds in the 24 weeks prior to study entry, which is not representative of patients with hemophilia A in Canadian clinical practice. As the study population in HAVEN 3 had greater uncontrolled bleeding than would be expected in Canadian practice, this may overstate the clinical efficacy of emicizumab compared to what would be expected in the clinical setting. The magnitude of the treatment effect in patients with better control (consistent with the Canadian clinical population) compared to those included in the trials remains unknown. Eligibility criteria further excluded patients who had thromboembolic disease, were at high risk for microangiopathy, or had certain autoimmune diseases, thereby decreasing generalizability to the Canadian clinical population. HAVEN 3 further excluded patients under the age of 12. According to clinical experts consulted by CADTH, patients as young as 1 year of age may be prescribed emicizumab.

- Given the clinical evidence base, CADTH was unable to conduct a reanalysis to adequately assess this limitation. To align with the clinical evidence, the age parameter in the model was revised to reflect the distribution reported in HAVEN 3. A scenario analysis was further conducted in which the patient age was set to 2 years, as assumed in the sponsor's model. Although evidence on the effects of emicizumab on children without inhibitors is lacking, the efficacy and safety of emicizumab should not be age-dependent, according to the clinical experts consulted by CADTH, given the known mechanism of action of emicizumab and the existing clinical evidence for emicizumab in children with inhibitors.
- **Naïve comparison for emicizumab versus FVIII prophylaxis:** Treatment efficacy in the sponsor's model was informed by the HAVEN 3 and the NIS.<sup>7</sup> The NIS preceded HAVEN 3 and was conducted among patients on FVIII prophylaxis. These patients were subsequently eligible for enrolment in HAVEN 3 in a separate, non-randomized arm, and received emicizumab prophylaxis.<sup>4</sup> For the emicizumab and on-demand groups in the economic model, clinical efficacy was informed by the appropriate randomized arms in the HAVEN 3 trial; for FVIII prophylaxis, clinical efficacy was informed by the NIS. It is inappropriate to compare clinical outcomes for FVIII prophylaxis in the NIS with the clinical outcomes for emicizumab in HAVEN 3. As the CADTH clinical report notes, there is no direct comparative evidence to support the efficacy of emicizumab compared to FVIII prophylaxis in patients with severe hemophilia A; the only evidence is limited to an intra-patient analysis (group D in HAVEN 3). The sponsor's approach reflects a non-randomized, naïve comparison; it remains unclear what potential biases are introduced into the economic analysis given this approach. Certain reported baseline characteristics were found to differ between the randomized HAVEN 3 groups and the NIS group: the NIS group was younger and had experienced a lower number of bleeds in the prior 24 weeks. Although the clinical experts consulted by CADTH noted that these baseline differences would be expected in the FVIII prophylaxis population, and that treatment effects are likely independent of patient age, it is unclear whether other biases could have been introduced through this non-randomized comparison. They also commented that while the clinical estimates used in the economic model likely represent the Canadian setting, they may lack precision. The sponsor further commissioned an indirect treatment comparison and incorporated these estimates into a scenario analysis. Although the sponsor's network meta-analysis suggested that emicizumab prophylaxis was associated with reduced bleed rates compared with FVIII prophylaxis in the treatment of patients with severe hemophilia A without inhibitors, methodological limitations of the indirect treatment comparison affect both the confidence of this finding and the appropriateness of using these estimates to inform the economic model. A small number of trials were included in the analysis, and each trial enrolled a small number of patients. Due to the small evidence base, the results of the analysis were uncertain. A high degree of heterogeneity was further noted across the included studies, including: the severity of hemophilia A; different FVIII products studied; inconsistent or unclear definitions of the bleed outcomes; variable time points for outcome measurement; and differences in study design. Together, these limitations preclude the use of estimates derived from the network meta-analysis to inform the comparative treatment effects of emicizumab relative to FVIII prophylaxis.
  - Given the lack of clinical literature comparing FVIII prophylaxis to emicizumab directly, CADTH was unable to conduct a reanalysis to assess this limitation. CADTH conducted a scenario analysis in which FVIII prophylaxis was removed as a comparator.
- **Dispensing of treatment does not reflect clinical practice.** In the sponsor's submitted economic model, treatment was dispensed according to the sponsor's product monographs, with treatment-acquisition costs calculated based on the exact dose (per mg) required. This misaligns with the assumptions stated in the sponsor's submitted budget impact analysis. The product monograph for emicizumab states that the drug is for single use only and available in pre-set concentrations. According to the CADTH clinical experts, patients on both emicizumab and FVIII would typically have their dose

rounded up to the nearest whole vial, with the drug dispensed accordingly to minimize wastage. How treatments are dispensed needs to be accounted for in the cost of treatment. In the sponsor's approach, the treatment-acquisition costs for both emicizumab and the FVIII comparators were underestimated.

- CADTH considered that dispensed drugs would be rounded up to the nearest whole vial to reflect clinical practice settings.
- **Inappropriate modelling of health-utility estimates.** The utility estimates were based on a sponsor's commissioned utility exercise in which a sample of the Canadian public ( $n = 82$ ) provided utility estimates based on a time trade-off vignette exercise.<sup>7</sup> Based on the survey responses, regression models were derived. The first model included treatment administration (subcutaneous versus intravenous) and the number of bleeds per year as predictor variables; using the same dataset, a second regression analysis was modelled specific to prophylaxis treatment with a single predictor: the frequency of infusions per year.

$$\text{Regression model 1: Utility} = 0.7966 - (0.0027 \times \text{bleeds per year}) + (0.1112 \times \text{subcutaneous})^a$$

<sup>a</sup> versus reference category of intravenous infusion

$$\text{Regression model 2: Utility} = 0.858 - 0.0003 \times \text{number of infusions per year}$$

The sponsor derived baseline utility for the treatment and comparator arms based on combining the coefficients from both regression analyses. This, in effect, introduces treatment-specific utility values (i.e., emicizumab = 0.908 [based on summing the intercept and the coefficient for subcutaneous treatment from the first regression model]; on-demand FVIII = 0.797 [based on the intercept from the first regression model]; and FVIII prophylaxis = 0.759 [based on the intercept from the first regression model subtracted from the product of the number of infusions and the disutility of infusion from the second regression model]).<sup>7</sup> This approach (i.e., combining values from separate regression equations) is inappropriate because these regressions are conceptually different and not compatible given that each regression equation is estimating a different set of estimates. Therefore, this approach lacks credibility. In effect, it applies 2 separate adjustments for IV infusions (i.e., 1 from each regression model) without consideration that the values from the separate regression equations are, in fact, correlated. As per current guidelines for the conduct of economic evaluations,<sup>9</sup> utilities should reflect the health states within the model and not be specific to treatment. Although an argument could potentially be made on patient preference for the mode of treatment administration, the sponsor's estimate would indicate that patients are willing to trade off 1.1 years of perfect health every 10 years to avoid treatments involving IV administration, assuming all else is considered equal. This magnitude is greater than the benefit that a patient with mild anemia achieves with treatment that fully resolves their anemia.<sup>11</sup> Of note, the CADTH clinical experts indicated that the effect of treatment on improved quality of life remains inconclusive.

- CADTH removed treatment-specific utility values by setting the baseline utility to be identical across all treatments. The utility decrements arising from treated bleeds and infusions were incorporated into the model separately. Given the limitations with the structure of the sponsor's submitted model, utility decrements could not be applied to adverse events.
- **Missing comparators.** The comparators in the submitted economic model reflected approaches to treating patients with hemophilia A with FVIII products. However, in consultation with the clinical experts, it was noted that plasma-derived von Willebrand factor (VWF) products, such as Antihemophilic Factor/ VWF Complex (Human) (Humate-P) and VWF/Coagulation Factor VIII Complex (Human) (Wilate), may also be used in this patient population. These comparators were not considered in the sponsor's submitted model.

- Given the lack of comparative clinical effectiveness data presented by the sponsor and the structure of the submitted economic model, CADTH was unable to conduct a reanalysis to assess this limitation.
- **Underestimation of adult patient weights.** Patient weights used in the model were sourced from UK life tables. Hemophilia A primarily affects men; men are, on average, heavier than women.<sup>12</sup> Furthermore, the average weight of patients in the HAVEN 3 trial (79.1kg)<sup>4</sup> was greater than the sponsor's assumption (75.2 kg). This difference in weight would translate to a different vial size for emicizumab and, thereby, a higher treatment-acquisition cost. Setting the weight at 75.2 kg would have underestimated the expected cost of emicizumab.
- CADTH set the average patient weight to reflect that reported in the HAVEN 3 trial.

One additional limitation was identified, but was considered unlikely to change or to affect the analyses significantly. This limitation is outlined next.

- **Disutility from arthroplasties was not included in the model.** As joint replacement due to severe bleeding events would affect quality of life, a disutility of 0.39 was applied for arthroplasties for the duration across which the model captured their impact.<sup>13</sup>

Additionally, the following key assumptions were made by the sponsor and have been appraised by CADTH (Table 4).

**Table 4: Key Assumptions of the Submitted Economic Evaluation (Not Noted as Limitations to the Submission)**

Sponsor's key assumption	CADTH comment
FVIII inhibitors were pooled, assuming similar efficacy, when defining model comparators.	According to the clinical experts consulted by CADTH, the efficacy and potential harms of FVIII inhibitors are likely similar. However, the costs of these products may differ. To establish the treatment-acquisition costs, a weighted approach was taken. In effect, the cost-effectiveness of emicizumab relative to individual FVIII inhibitor products is unknown.
The cost and impact of a treated bleed event were assumed to be similar (i.e., no difference by severity and type of bleeding event).	Inappropriate. According to clinical experts, the amount of prophylaxis needed to treat a bleed is dependent on the location and severity of the bleed.
Perfect adherence was assumed. <sup>a</sup>	This is an acceptable and conservative assumption. Among patients eligible for an analysis of adherence to FVIII prophylaxis in arm D of HAVEN 3, 34% reported receiving fewer than 80% of prescribed doses. <sup>4</sup>
The model assumed that no patients treated with emicizumab or FVIII prophylaxis would require arthroplasty, while patients treated with on-demand therapy would experience 2 arthroplasties over the course of their lifetimes.	Clinical experts have stated that arthroplasties are a result of poor disease management and not a result of treatment. On-demand therapy often leads to suboptimal management of hemophilia A. The number of arthroplasties in a lifetime is uncertain, but the model is not sensitive to this assumption.
The standardized mortality ratio for mild and moderate hemophilia was applied to patients on emicizumab and FVIII prophylaxis, while the standardized mortality ratio for severe hemophilia was applied to patients using on-demand FVIII. <sup>6</sup>	Uncertain. No deaths were reported in the HAVEN 3 or HAVEN 4 trials. <sup>4,14</sup> However, the model is not sensitive to this assumption.
The adverse-events profile reported in adult and adolescent patients (aged > 12) with hemophilia A with FVIII inhibitors would be similar to the expected adverse-event profile for patients with hemophilia A without FVIII inhibitors.	Given that the HAVEN 3 trial did not report any grade 3 or grade 4 treatment-related adverse events, <sup>b</sup> the sponsor's submitted model used the adverse-event profile reported in HAVEN 1. <sup>4,5</sup> HAVEN 1 investigated patients with FVIII inhibitors, some of whom had vascular access devices; the adverse events experienced included those related to the devices. <sup>5</sup> According to the clinical

Sponsor's key assumption	CADTH comment
	experts consulted, the rate of adverse events in a population without FVIII inhibitors is likely lower than the rate in a population with FVIII inhibitors. This indicates that the sponsor's approach overestimated adverse events. Although the incidence of adverse events was higher in the comparator arms, the sponsor's model was not sensitive to parameters relating to adverse events.
All treatments would be administered at home.	Appropriate.

<sup>a</sup> Adherence is defined as the extent to which a patient is administered their prescribed dose at the recommended dosing frequency.

<sup>b</sup> HAVEN 3 reported grade  $\geq 3$  treatment-emergent adverse events. These were not included in the sponsor's economic model.

## CADTH Reanalyses of the Economic Evaluation

### Base-Case Results

While several limitations with the sponsor's submission could not be addressed (i.e., model structure, patient population, noncomparative clinical outcomes for FVIII prophylaxis, and missing comparators), other limitations could be explored. CADTH undertook a stepped analysis, incorporating each change detailed in Table 5 into the sponsor's corrected base case to highlight the impact of each change. The summary results of the sponsor's corrected base case and the CADTH reanalyses are presented in Table 6.

**Table 5: CADTH Revisions to the Submitted Economic Evaluation**

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
<b>Corrections<sup>a</sup> to the sponsor's base case</b>		
Value/formula within Cell "I63", from Excel worksheet entitled " <i>Model Input</i> "	Deterministic input: "2.69"	Probabilistic input: "= IF(psa = 1, R63, M63)"
<b>Changes to derive the CADTH base case</b>		
1. Model's starting age	All patients entered the model at age 2 years	Defined by a probabilistic distribution consistent with the HAVEN 3 trial population (mean = 39.8; standard deviation = 14) <sup>4</sup>
2. Treatment dispensing	Dispensed to the exact dose (by mg)	Dispensed to the nearest vial size
3. Baseline utility	FVIII prophylaxis = 0.759, FVIII on-demand = 0.797, and emicizumab = 0.908	Baseline utility (across all treatments) = 0.908
4. Patients' weight (adults)	75.2 kg	79.1 kg
5. Disutility associated with arthroplasty	No disutility from arthroplasty	Disutility of 0.39 associated with arthroplasty across 30 days

In the CADTH base case, emicizumab was associated with an additional cost of \$8,691,419 and 1.57 additional QALYs, for an ICER of 5,530,766 per QALY gained compared to FVIII prophylaxis. Using a willingness-to-pay threshold of \$50,000 per QALY, there is a 0% probability that emicizumab would be considered cost-effective in the CADTH base case. This is primarily due to the incorporation of vial wastage and removing treatment-specific utility values.

Detailed results of the CADTH base case are presented in Table 12 of Appendix 4. Of note, the reanalysis is based on publicly available prices of the comparator treatments.

**Table 6: Summary of the Stepped Analysis of the CADTH Reanalysis Results**

Stepped analysis	Drug	Total costs (\$)	Total QALYs	Sequential ICER (\$/QALYs)
<b>Sponsor's base case</b>	On-demand treatment	3,907,944	25.4	—
	FVIII prophylactic treatment	20,116,294	33.0	<i>Extended dominance</i>
	Emicizumab	28,750,976	40.4	1,657,813
<b>Sponsor's corrected base case</b>	On-demand treatment	3,924,139	25.4	—
	Emicizumab	28,749,181	40.4	1,653,834
	FVIII prophylactic treatment	20,115,810	33.0	<i>Extended dominance</i>
<b>CADTH reanalysis 1 (model's starting age)</b>	On-demand treatment	2,885,705	15.47	—
	FVIII prophylactic treatment	15,967,809	21.91	<i>Extended dominance</i>
	Emicizumab	23,185,020	26.80	1,792,779
<b>CADTH reanalysis 2 (treatment dispensing)</b>	On-demand treatment	3,947,354	25.32	—
	FVIII prophylactic treatment	24,158,266	33.01	<i>Extended dominance</i>
	Emicizumab	34,804,018	40.38	2,049,919
<b>CADTH reanalysis 3 (baseline utility)</b>	On-demand treatment	3,892,629	30.08	—
	FVIII prophylactic treatment	20,115,870	38.02	2,043,454
	Emicizumab	28,752,144	40.40	3,630,741
<b>CADTH reanalysis 4 (patient weight)</b>	On-demand treatment	4,046,393	25.35	—
	FVIII prophylactic treatment	20,724,997	33.01	<i>Extended dominance</i>
	Emicizumab	29,622,261	40.38	1,702,396
<b>CADTH reanalysis 5 (arthroplasty disutility)</b>	On-demand treatment	3,916,796	25.40	—
	FVIII prophylactic treatment	20,116,566	33.01	<i>Extended dominance</i>
	Emicizumab	28,752,416	40.38	1,658,289
<b>CADTH base case (reanalyses 1 to 5)</b>	On-demand treatment	2,983,005	18.23	—
	FVIII prophylactic treatment	18,871,538	25.15	2,298,545
	Emicizumab	27,562,957	26.72	5,530,766

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

### Scenario Analysis Results

Several scenario and sensitivity analyses were conducted on the CADTH base case. These scenario analyses primarily explored changes in starting age, drug prices, and utility. Furthermore, scenario analyses included testing a structural assumption in which patients on FVIII treatments could be at risk of developing inhibitors and a scenario in which FVIII prophylaxis was removed as a possible comparator in light of the noncomparative evidence available. The model interpretations were found to remain robust (Table 13) because no scenario brought the sequential ICER of emicizumab close \$50,000 per QALY.

The model was most sensitive to the price of the comparator treatment. The public prices for FVIII, reported by PMPRB are ceiling prices (i.e., they reflect the maximum average potential price). Utilizing these prices in the model, a price reduction of at least 89% is required for emicizumab to be considered cost-effective at a willingness-to-pay threshold of \$50,000 per QALY, according to the CADTH base case (Table 7). Given that PMPRB prices may not reflect the actual price of FVIII products in Canada, 2-way price-reduction analyses were further conducted to highlight the influence of price reduction on the cost-effectiveness results for both emicizumab and FVII (Table 8).

**Table 7: CADTH Price-Reduction Analyses**

ICERs for emicizumab versus FVIII comparators		
Price reduction of emicizumab	Sponsor-corrected base case (\$/QALY)	CADTH reanalysis (\$/QALY)
<b>None</b>	If $\lambda < \$1.6M$ , on-demand. <b>If <math>\lambda \geq \\$1.6M</math>, emicizumab.</b> .	If $\lambda < \$2.3M$ , on-demand. If $\$2.3M \leq \lambda < \$5.5M$ , FVIII prophylaxis. <b>If <math>\lambda \geq \\$5.5M</math>, emicizumab.</b>
<b>10%</b>	If $\lambda < \$1.5M$ , on-demand. <b>If <math>\lambda \geq \\$1.5M</math>, emicizumab.</b>	If $\lambda < \$2.3M$ , on-demand. If $\$2.3M \leq \lambda < \$3.8M$ , FVIII prophylaxis. <b>If <math>\lambda \geq \\$3.8M</math>, emicizumab.</b>
<b>20%</b>	If $\lambda < \$1.3M$ , on-demand. <b>If <math>\lambda \geq \\$1.3M</math>, emicizumab.</b>	If $\lambda < \$2.3M$ , on-demand. <b>If <math>\lambda \geq \\$2.3M</math>, emicizumab.</b>
<b>30%</b>	If $\lambda < \$1.1M$ , on-demand. <b>If <math>\lambda \geq \\$1.1M</math>, emicizumab.</b>	If $\lambda < \$1.9M$ , on-demand. <b>If <math>\lambda \geq \\$1.9M</math>, emicizumab.</b>
<b>40%</b>	If $\lambda < \$900K$ , on-demand. <b>If <math>\lambda \geq \\$900K</math>, emicizumab.</b>	If $\lambda < \$1.6M$ , on-demand. <b>If <math>\lambda \geq \\$1.6M</math>, emicizumab.</b>
<b>50%</b>	If $\lambda < \$707K$ , on-demand. <b>If <math>\lambda \geq \\$707K</math>, emicizumab.</b>	If $\lambda < \$1.3M$ , on-demand. <b>If <math>\lambda \geq \\$1.3M</math>, emicizumab.</b>
<b>60%</b>	If $\lambda < \$521K$ , on-demand. <b>If <math>\lambda \geq \\$521K</math>, emicizumab.</b>	If $\lambda < \$973K$ , on-demand. <b>If <math>\lambda \geq \\$973K</math>, emicizumab.</b>
<b>70%</b>	If $\lambda < \$331K$ , on-demand. <b>If <math>\lambda \geq \\$331K</math>, emicizumab.</b>	If $\lambda < \$652K$ , on-demand. <b>If <math>\lambda \geq \\$652K</math>, emicizumab.</b>
<b>80%</b>	If $\lambda < \$142K$ , on-demand. <b>If <math>\lambda \geq \\$142K</math>, emicizumab.</b>	If $\lambda < \$327K$ , on-demand. <b>If <math>\lambda \geq \\$327K</math>, emicizumab.</b>
<b>89%</b>	<b>Emicizumab dominates both comparators</b>	If $\lambda < \$33K$ , on-demand. <b>If <math>\lambda \geq \\$33K</math>, emicizumab.</b>
<b>90%</b>	<b>Emicizumab dominates both comparators</b>	If $\lambda < \$3K$ , on-demand. <b>If <math>\lambda \geq \\$3K</math>, emicizumab.</b>

ICER = incremental cost-effectiveness ratio; FVIII = factor VIII;  $\lambda$  = willingness-to-pay threshold; M = million; K = thousand.

**Table 8: CADTH 2-Way Price-Reduction Analyses**

Price of FVIII products	Price of emicizumab					
		No reduction	25% reduction	50% reduction	75% reduction	90% reduction
<b>No reduction</b>	If $\lambda < \$2.3M$ , on-demand. If $\$2.3M \leq \lambda < \$5.5M$ , FVIII prophylaxis. <b>If <math>\lambda \geq \\$5.5M</math>, emicizumab.</b>	If $\lambda < \$1.8M$ , on-demand. <b>If <math>\lambda \geq \\$1.8M</math>, emicizumab.</b>	If $\lambda < \$1.3M$ , on-demand. <b>If <math>\lambda \geq \\$1.3M</math>, emicizumab.</b>		If $\lambda < \$456K$ , on-demand. <b>If <math>\lambda \geq \\$456K</math>, emicizumab.</b>	If $\lambda < \$37K$ , on-demand. <b>If <math>\lambda \geq \\$37K</math>, emicizumab.</b>
<b>25% reduction</b>	If $\lambda < \$1.9M$ , on-demand. If $\$1.9M \leq \lambda < \$8.2M$ , FVIII prophylaxis. <b>If <math>\lambda \geq \\$8.2M</math>, emicizumab.</b>	If $\lambda < \$1.8M$ , on-demand. If $\$1.8M \leq \lambda < \$3.8M$ , FVIII prophylaxis. <b>If <math>\lambda \geq \\$3.8M</math>, emicizumab.</b>	If $\lambda < \$1.5M$ , on-demand. <b>If <math>\lambda \geq \\$1.5M</math>, emicizumab.</b>		If $\lambda < \$535K$ , on-demand. <b>If <math>\lambda \geq \\$535K</math>, emicizumab.</b>	If $\lambda < \$73K$ , on-demand. <b>If <math>\lambda \geq \\$73K</math>, emicizumab.</b>
<b>50% reduction</b>	If $\lambda < \$1.1M$ , on-demand. If $\$1.1M \leq \lambda < \$10.8M$ , FVIII prophylaxis. <b>If <math>\lambda \geq \\$10.8M</math>, emicizumab.</b>	If $\lambda < \$1.1M$ , on-demand. If $\$1.1M \leq \lambda < \$6.5M$ , FVIII prophylaxis. <b>If <math>\lambda \geq \\$6.5M</math>, emicizumab.</b>	If $\lambda < \$1.4M$ , on-demand. If $\$1.4M \leq \lambda < \$2.1M$ , FVIII prophylaxis. <b>If <math>\lambda \geq \\$2.1M</math>, emicizumab.</b>		If $\lambda < \$457K$ , on-demand. <b>If <math>\lambda \geq \\$457K</math>, emicizumab.</b>	If $\lambda < \$146K$ , on-demand. <b>If <math>\lambda \geq \\$146K</math>, emicizumab.</b>
<b>75% reduction</b>	If $\lambda < \$13.5M$ , on-demand. If $\$13.5M \leq \lambda < \$10.8M$ , FVIII prophylaxis. <b>If <math>\lambda \geq \\$10.8M</math>, emicizumab.</b>	If $\lambda < \$877K$ , on-demand. If $\$877K \leq \lambda < \$8.0M$ , FVIII prophylaxis. <b>If <math>\lambda \geq \\$8.0M</math>, emicizumab.</b>	If $\lambda < \$790K$ , on-demand. If $\$790K \leq \lambda < \$4.7M$ , FVIII prophylaxis. <b>If <math>\lambda \geq \\$4.7M</math>, emicizumab.</b>		If $\lambda < \$630K$ , on-demand. <b>If <math>\lambda \geq \\$630K</math>, emicizumab.</b>	If $\lambda < \$233K$ , on-demand. <b>If <math>\lambda \geq \\$233K</math>, emicizumab.</b>
<b>90% reduction</b>	If $\lambda < \$533K$ , on-demand. If $\$533K \leq \lambda < \$14.9M$ , FVIII prophylaxis. <b>If <math>\lambda \geq \\$14.9M</math>, emicizumab.</b>	If $\lambda < \$508K$ , on-demand. If $\$508K \leq \lambda < \$10.6M$ , FVIII prophylaxis. <b>If <math>\lambda \geq \\$10.6M</math>, emicizumab.</b>	If $\lambda < \$398K$ , on-demand. If $\$398K \leq \lambda < \$6.4M$ , FVIII prophylaxis. <b>If <math>\lambda \geq \\$6.4M</math>, emicizumab.</b>		If $\lambda < \$479K$ , on-demand. If $\$479K \leq \lambda < \$2.0M$ , FVIII prophylaxis. <b>If <math>\lambda \geq \\$2.0M</math>, emicizumab.</b>	If $\lambda < \$221K$ , on-demand. <b>If <math>\lambda \geq \\$221K</math>, emicizumab.</b>

$\lambda$  = willingness-to-pay threshold; M = million; K = thousand.

## Issues for Consideration

- Emicizumab is administered subcutaneously, whereas FVIII therapies are administered intravenously. According to the clinical experts consulted, both treatments can be administered at home following adequate patient training.
- According to the clinical experts consulted by CADTH and the health care provider input received as part of the patient group's feedback, adherence is key to reducing breakthrough bleeds that require treatment. The efficacy of treatment is highly dependent on patient adherence. It is plausible that emicizumab may result in better adherence to treatment, given its mode of administration and less frequent administration. Adherence, which would be expected to affect both costs and utilities, was not explicitly captured in the sponsor's model.
- CADTH was unable to adequately assess the impact of potentially lower prices of the comparators on the cost-effectiveness of emicizumab. Reduced effective prices for comparators, arising from the tendering process by Canadian Blood Services<sup>15</sup> (as opposed to PMPRB's maximum average potential price), may lead to different conclusions than the current analysis, potentially resulting in an even higher ICER for emicizumab.
- The development of neutralizing anti-drug antibodies in patients was not reported in the HAVEN 3 trial, although case reports have been observed in practice.<sup>16</sup> The clinical effects of anti-drug antibodies remain unclear, and their impact on both clinical effectiveness and cost-effectiveness remains unknown.
- Emicizumab has been reviewed by other Health Technology Assessment agencies. Quebec's Institut national d'excellence en santé et services sociaux has not recommended the reimbursement of emicizumab for patients without FVIII inhibitors.<sup>17</sup> A draft report from the Institute for Clinical and Economic Review found emicizumab is likely not cost-effective at a threshold of US\$200,000 per QALY for patients without FVIII inhibitors.<sup>18</sup>
- According to the clinical experts consulted by CADTH, there are several emerging treatments for patients with hemophilia that are currently under development or emerging. These include extended half-life factor replacement products, non-factor therapies (e.g., anti-tissue pathway inhibitor antibody), and gene therapies (e.g., valoctocogene roxaparvovec).<sup>19</sup>
- With respect to desmopressin's place in therapy, the clinical experts consulted by CADTH noted that it is primarily used to treat patients with mild or moderate hemophilia A.

## Overall Conclusions

Based on the CADTH clinical review of 2 sponsor-submitted trials (i.e., HAVEN 3 and HAVEN 4), emicizumab is associated with a statistically and clinically significantly improvement in bleeding outcomes (i.e., ATBR ratio for treated bleeds, all bleeds, treated joint bleeds, treated spontaneous bleeds) compared to on-demand treatment. Limited comparative evidence exists to establish the comparative effectiveness and safety of emicizumab compared to FVIII prophylaxis; however, current evidence suggests that emicizumab showed a reduction in bleeding outcomes compared to no prophylaxis (non-randomized comparison). No additional studies met the inclusion criteria for the systematic review conducted in the CADTH clinical review, and there is presently no clinical evidence comparing emicizumab to plasma-derived VWF products that could be used in this patient population. These limitations in clinical evidence could not be addressed in the pharmacoeconomic analysis.

Furthermore, CADTH could not address the limitations associated with the model structure and the analysis target population (compared with the intended population). The model target population is specific to patients with severe hemophilia A who meet HAVEN 3's eligibility criteria. The CADTH reanalysis was able to address only a subset of the limitations in the sponsor's submission, including: adjusting dispensing to the nearest vial size, removing treatment-specific utility estimates, and setting patients' starting age and weight to better reflect the patient population in HAVEN 3. CADTH's findings remained aligned with the sponsor's: emicizumab is not a cost-effective option at a willingness-to-pay threshold of \$50,000 per QALY in patients with severe hemophilia A. In the CADTH base-case reanalysis, the ICER for emicizumab was \$5,530,766 per QALY compared with FVIII prophylaxis. A price reduction of at least 89% is necessary for emicizumab to be considered cost-effective at a threshold of \$50,000 per QALY. However, a greater price reduction may be required if the price of FVIII products is, in fact, lower than the PMPRB published values.

The cost-effectiveness of emicizumab in both the reimbursement-requested population and the broader Health Canada indication remain unknown.

## Appendix 1: Cost-Comparison Table

The comparators presented in the following table have been to be deemed appropriate based on feedback from clinical experts. Comparators may be recommended (appropriate) practice or actual practice. Existing Product Listing Agreements are not reflected in the table and as such, the table may not represent the actual costs to public drug plans.

**Table 9: CADTH Cost-Comparison Table for Prophylaxis of Bleeding in Patients With Hemophilia A Without Factor VIII Inhibitors**

Treatment	Strength	Form	Price per unit (\$)	Recommended dosage	Daily cost (\$)	Course or annual cost (\$)
Emicizumab (Hemlibra)	30.0 mg/1.0 mL  60.0 mg/0.40 mL  105.0 mg/0.7 mL  150.0 mg/1.0 mL	Vial for SC injection	122.0506 per mg <sup>a</sup>	Loading dose: 3.0 mg/kg once weekly for 4 weeks  Maintenance dose: 1.5 mg/kg once weekly or 3.0 mg/kg every 2 weeks or 6.0 mg/kg every 4 weeks, starting week 5 for patients $\geq$ 12 years of age who weigh $\geq$ 40 kg. Patients under 12 years or those who weigh < 40kg should receive 1.5 mg/kg every week or 3.0 mg/kg every 2 weeks starting week 5.	40 kg patient: Loading: 2,092.30 Maintenance: 1,046.15  80 kg patient: Loading: 4,184.59 Maintenance: 2,092.30	40 kg patient: Year 1: 411,136 Thereafter: 381,841  80 kg patient: Year 1: 822,272 Thereafter: 763,688
<b>Factor VIII treatments available through Canadian Blood Services</b>						
Antihemophilic Factor (Recombinant), PEGylated (Adynovate)	250 IU 500 IU 750 IU 1,000 IU 1,500 IU 2,000 IU 3,000 IU	Powder for IV injection	1.8862 per IU <sup>b</sup>	Patients < 12 years: 40 IU/kg to 60 IU/kg twice weekly  Patients $\geq$ 12 years: 40 IU/kg to 50 IU/kg twice weekly	40 kg patient: 943.10 to 1,077.83  80 kg patient: 1,751.47 to 2,694.57	40 kg patient: 344,232 to 393,407  80 kg patient: 639,287 to 983,519
Antihemophilic Factor (Recombinant) BDD, Fc Fusion Protein (Eloctate)	250 IU 500 IU 750 IU 1,000 IU 1,500 IU	Powder for IV injection	1.8862 per IU <sup>c</sup>	50 IU/kg every 3 to 5 days	40 kg patient: 754.48 to 1,257.47  80 kg patient:	40 kg patient: 275,385 to 458,975  80 kg patient:

Treatment	Strength	Form	Price per unit (\$)	Recommended dosage	Daily cost (\$)	Course or annual cost (\$)
	2,000 IU 3,000 IU				1,508.96 to 2,514.93	550,770 to 917,951
Antihemophilic Factor (Recombinant) BDD, PEGylated (Jivi)	250 IU 500 IU 1,000 IU 2,000 IU 3,000 IU	Vial	1.8862 per IU <sup>b</sup>	Patients ≥ 12 years: 30 IU/kg to 40 IU/kg twice weekly	40 kg patient: 673.64 to 943.10 80 kg patient 1,347.29 to 1,751.47	40 kg patient: 245,880 to 344,232 80 kg patient: 491,759 to 639,287
Antihemophilic Factor (Recombinant) (Kovaltry)	250 IU 500 IU 1,000 IU 2,000 IU 3,000 IU	Vial	1.4592 per IU <sup>c</sup>	Patients ≤ 12 years: 20 IU/kg to 50 IU/kg, 2 to 3 times weekly or every other day  Patients > 12 years: 20 IU/kg to 40 IU/kg, 2 to 3 times weekly	40 kg patient : (≤ 12) 416.91 to 1,459.20  80 kg patient: 729.60 to 2,032.46	40 kg patient: (≤ 12) 152,174 to 532,608  80 kg patient: 266,304 to 741,847
Antihemophilic Factor (Recombinant) BDD, (Nuwiq)	250 IU 500 IU 1,000 IU 2,000 IU 2,500 IU 3,000 IU 4,000 IU	Powder and solvent for IV injection	287.2426 <sup>c</sup> 559.0977 <sup>c</sup> Unknown Unknown Unknown 3,823.5677 <sup>c</sup> 5,098.0903 <sup>c</sup>	Children <sup>d</sup> : 30 IU/kg to 40 IU/kg every other day or 3 times weekly  Adults: 30 IU/kg to 40 IU/kg every other day	40 kg patient (child): 399.36 to 838.65 <sup>e</sup>  80 kg patient: 798.71 to 1,038.32 <sup>e</sup>	40 kg patient (child): 145,765 to 306,106 <sup>e</sup>  80 kg patient: 291,530 to 378,988 <sup>e</sup>
Antihemophilic Factor (Recombinant)BDD rFVIII (Xyntha)	250 IU 500 IU 1,000 IU 2,000 IU	Powder in vial	1.1182 per IU <sup>f</sup>	Adults and adolescents <sup>g</sup> : 30 IU/kg ± 5 IU/kg 3 times weekly	40 kg patient: 479.23 to 718.84  80 kg patient: 958.45 to 1,437.68	40 kg patient: 174,918 to 262,377  80 kg patient: 349,835 to 524,753
<b>Factor VIII and von Willebrand factor treatments available through Canadian Blood Services</b>						
Antihemophilic Factor/VWF Complex (Human) (Humate-P)	250/600 IU 500/1,200 IU 1,000/2,400 IU	Vial for IV injection	1.1182 per IU <sup>f</sup>	Not indicated for prophylaxis. Depends on severity of bleed. Loading doses may be 15 IU/kg to 50 IU/kg, followed by additional doses of approximately half the loading dose, 1 to 3 times daily for up to 14 days.	40 kg patient: Loading dose: 838.65 to 2,236.39  80 kg patient: Loading dose: 1,397.74 to 3,913.68	NA

Treatment	Strength	Form	Price per unit (\$)	Recommended dosage	Daily cost (\$)	Course or annual cost (\$)
VWF/Coagulation Factor VIII Complex (Human) (Wilate)	500/500 IU 1,000/1,000 IU	Powder and solvent for IV injection	1.1182 per IU <sup>f</sup>	20 IU/kg every 2 to 3 days	40 kg patient: 372.73 to 559.10  80 kg patient: 745.47 to 1,118.20	40 kg patient: 136,048 to 204,072  80 kg patient: 272,095 to 408,143
<b>Desmopressin</b>						
Desmopressin (Deamino D-arginine Vasopressin)	4 mcg/mL	Vial for injection	10.9800 per mL <sup>h</sup>	Not indicated for prophylaxis. 0.3 mcg/kg by IV infusion; maximum dose 20 mcg	40 kg patient: 32.94 per use  80 kg patient: 54.90 per use	NA

BDD = B-domain deleted; FVIII = factor VIII; IU = international unit; IV = intravenous; NA = not applicable; PMPRB = Patented Medicine Prices Review Board; FVIII = factor VIII; SC = subcutaneous; VWF = von Willebrand factor.

Note: Daily and annual costs are rounded up to the nearest available vial size; patients typically administer the full amount in the vial for factor VIII products, according to the clinical experts consulted by CADTH. PMPRB pricing represents the maximum average potential price in Canada; it is likely that due to the Canadian Blood Services tendering system, actual costs per international unit are substantially lower.

<sup>a</sup> Sponsor's submitted price.

<sup>b</sup> The price for Jivi was unavailable from PMPRB. The price for Eloctate was used as the lowest available long-acting proxy.

<sup>c</sup> PMPRB maximum average potential price, accessed September 2020.<sup>20</sup>

<sup>d</sup> The term "children" is not defined in the dosage and administration section of the Nuwiq product monograph; however, other sections specify that pediatric studies were conducted in patients ≤ 12 years of age.<sup>21</sup>

<sup>e</sup> The lowest cost per international unit across available strengths of Nuwiq of \$1.1182 was assumed in daily and annual cost calculations.<sup>20</sup>

<sup>f</sup> Price unavailable from PMPRB. Nuwiq price was used as a proxy price.<sup>20</sup>

<sup>g</sup> Xyntha is deemed appropriate for children of all ages, including newborns, in the product monograph; however, no dosing information is provided for prophylactic use in pre-adolescent children.<sup>22</sup>

<sup>h</sup> The Saskatchewan Formulary (accessed August 2020).<sup>23</sup>

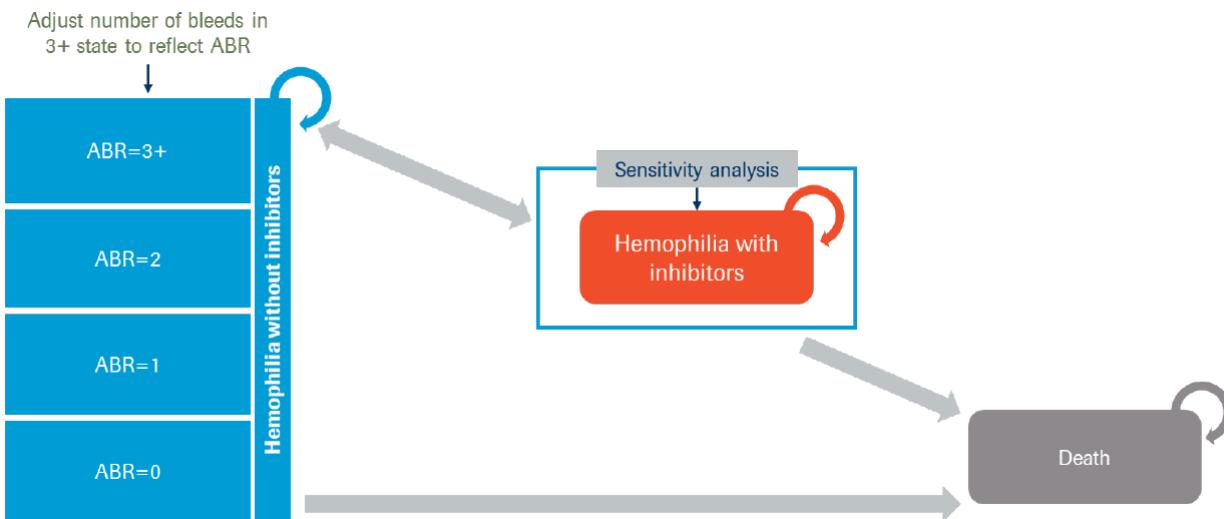
## Appendix 2: Submission Quality

**Table 10: Submission Quality**

Description	Yes	No	Comments
Population is relevant, with no critical intervention or relevant outcome missing.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	The modelled population did not reflect either the Health Canada indication nor the sponsor's requested-reimbursement indication.
Model has been adequately programmed and has sufficient face validity.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Model structure is adequate for decision problem.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	See key limitation section.
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis).	<input type="checkbox"/>	<input checked="" type="checkbox"/>	The model assumed treatment-specific utilities.
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	The number of treated bleeds that a patient experiences each year was included in the model as a fixed proportion.
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough details).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

## Appendix 3: Additional Information on the Submitted Economic Evaluation

**Figure 1: Model Structure**

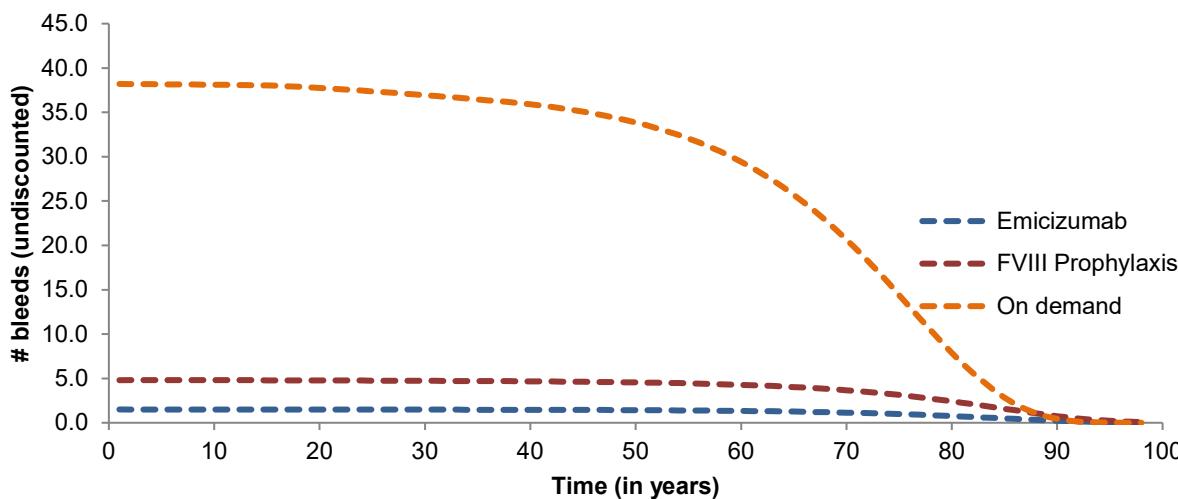


ABR = annualized (treated) bleed rate. The sponsor used ABR to refer to annualized treated bleed rate in this instance.

Source: Sponsor's pharmacoeconomic submission.<sup>8</sup>

The model estimates that patients receiving on-demand treatment will experience 30 to 40 bleed events, while patients receiving emicizumab will experience nearly 0 bleed events on average (Figure 2).

**Figure 2: Number of Bleeds per Year**



FVIII = factor VIII.

Source: Sponsor's pharmacoeconomic submission.<sup>8</sup>

**Table 11: Number of Bleeds Experienced in a Year per Treatment Arm**

Number of bleeds per year	Emicizumab	FVIII prophylaxis	On-demand therapy
<b>0 bleeds (%)</b>	41.70	31.30	0.00
<b>1 bleed (%)</b>	14.60	12.50	0.00
<b>2 bleeds (%)</b>	8.30	4.20	0.00
<b>3 bleeds (%)</b>	35.40	52.10	100.00
<b>Overall annual bleed rate</b>	1.50	4.80	38.20
<b>Number of bleeds for ≥ 3 bleeds</b>	3.356	8.812	38.20

Source: Sponsor's pharmacoeconomic submission (Table 3).<sup>8</sup>

## Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

**Table 12: Disaggregated Summary of CADTH's Economic Evaluation Results**

Treatment	Component	Value	Incremental (versus on-demand therapy)	Incremental (sequential)	Percentage of total incremental (sequential)
<b>Discounted QALYs</b>					
On-demand therapy		18.23	NA	NA	NA
FVIII prophylaxis		25.15	6.91	NA	NA
Emicizumab		26.72	8.48	1.57	5.88%
<b>Discounted costs (\$)</b>					
On-demand therapy	Acquisition	0	NA	NA	NA
	Physician visits (hospitalization + bleed treatment)	2,975,173	NA	NA	NA
	AEs (including arthroplasty)	7,832	NA	NA	NA
	Total	2,983,005	NA	NA	NA
FVIII prophylaxis	Acquisition	17,963,685	17,963,685	NA	NA
	Physician visits (hospitalization + bleed treatment)	904,770	-2,070,403	NA	NA
	AEs (including arthroplasty)	3,082	-4,750	NA	NA
	Total	18,871,538	15,888,533	NA	NA
Emicizumab	Acquisition	27,271,318	27,271,318	9,307,633	34.13%
	Physician visits (hospitalization + bleed treatment)	290,204	-2,684,969	-614,566	-47.22%
	AEs (including arthroplasty)	1,435	-6,398	-1,647	-87.13%
	Total	27,562,957	24,579,952	8,691,419	31.53%
<b>ICER vs. reference (\$/QALY)</b>			<b>Sequential ICER (\$/QALY)</b>		
On-demand therapy		NA	NA		
FVIII prophylaxis		2,298,545	2,298,545		
Emicizumab		2,895,165	5,530,766		

AE = adverse event; ICER = incremental cost-effectiveness ratio; LY = life-year; NA = not applicable; QALY = quality-adjusted life-year; vs. = versus.

**Table 13: Sensitivity and Scenario Analysis Results**

Scenario	Sponsor's value	CADTH base-case value	Sensitivity or scenario value	Emicizumab sequential ICER (\$/QALY)
CADTH base case				
Drug acquisition cost of FVIII products set to cheapest available option (\$/IU)	Eloctate = \$1.8862 Adynovate = \$1.8862 Kovaltry = \$1.4592 Nuwiq = \$1.1182 Xyntha = \$1.1182	Same as sponsor	All FVIII products = 1.1182	5,530,766 vs. FVIII prophylaxis
Baseline utility estimates reflect on-demand FVIII value from the sponsor's de novo study	FVIII prophylaxis = 0.759 FVIII on-demand = 0.797 Emicizumab = 0.908	Base utility (across all treatments) = 0.908	FVIII prophylaxis = 0.759 FVIII on-demand = 0.797 Emicizumab = 0.908	8,663,049 vs. FVIII prophylaxis
Disutility from treated bleed events and drug administration (per event) increased by 10%	Bleed disutility = 0.003 Infusion disutility = 0.0003	Same as sponsor	Bleed disutility = 0.0033 Infusion disutility = 0.00033	2,295,269 vs. on-demand therapy
Starting age	2 years	Mean = 39.8 (SD: 14)	2	5,015,909 vs. FVIII prophylaxis
Potential for inhibitor development	Patients could not develop FVIII inhibitors	Same as sponsor	Patients could potentially develop FVIII inhibitors	4,488,208 vs. FVIII prophylaxis
Removing FVIII prophylaxis as comparator	Regular treatment with FVIII prophylaxis was included as a comparator	Same as sponsor	Regular treatment with FVIII prophylaxis was not included as a comparator	3,678,697 vs. FVIII prophylaxis
				2,897,247 vs. on-demand therapy

FVIII = factor VIII; SD = standard deviation; vs. = versus.

## Appendix 5: Submitted Budget Impact Analysis and CADTH Appraisal

### Key take-aways of the BIA

- CADTH identified the following key limitations with the sponsor's analysis:
  - Because the actual cost of FVIII products is confidential, there is significant uncertainty in the price of FVIII comparators. This uncertainty is likely to favour the adoption of emicizumab.
  - The adult weights used were not representative of the Canadian or trial populations.
  - ATBRs in the severe, on-demand population are unlikely to be representative of the Canadian context.
  - The uptake of emicizumab across patient groups is uncertain.
  - The distribution of patients currently receiving FVIII prophylaxis versus on-demand treatment is unknown.
- The CADTH reanalyses included: assuming patients with severe hemophilia A on on-demand therapy have an ATBR of 24.1; and changing the adult weight to be consistent with the average weight observed in the HAVEN 3 trial (79.1 kg).<sup>24</sup>
- The sponsor's budget impact analysis (BIA) population was aligned with the sponsor's reimbursement request: patients with severe hemophilia A without FVIII inhibitors; patients at significant risk for increased bleeding rates due to factors that lead to poor adherence or persistence (despite being candidates for routine prophylaxis with FVIII); and patients who have limited ability to receive regular IV therapy. Based on the CADTH reanalyses, the budget impact from the introduction of emicizumab for the sponsor's reimbursement request is expected to be \$73,091,035 in year 1, \$77,522,044 in year 2, and \$88,989,541 in year 3, with a 3-year total budget impact of \$239,602,620. Uncertainty remains regarding comparator pricing, the expected uptake of emicizumab, and the distribution of patients across currently available therapies. Results appear to be driven mostly by the price of FVIII and the price of emicizumab.

### Summary of Sponsor's Business Impact Analysis

In the submitted BIA, the sponsor assessed the introduction of prophylactic emicizumab for the treatment of patients with hemophilia A without factor VIII (FVIII) inhibitors compared to prophylactic or on-demand treatment with FVIII replacement therapy, consistent with the requested reimbursement criteria (see Table 1). The BIA was undertaken from the perspective of a Canadian public payer over a 3-year time horizon using an epidemiological approach. The sponsor included the acquisition costs associated with plasma protein products, including wastage, but excluded mark-ups and dispensing fees (Table 14). Data for the model were obtained from various sources, including the HAVEN 3 and 4 trials,<sup>14,24</sup> the Canadian Blood Disorders Registry,<sup>25</sup> published literature, CADTH's 2015 budget impact analysis for Eloctate,<sup>26</sup> and expert opinion.<sup>8</sup>

**Table 14: Summary of Key Model Parameters**

Parameter	Sponsor's estimate (reported as year 1, year 2, and year 3, if appropriate)
<b>Target population</b>	
• Patients with hemophilia A (congenital FVIII deficiency) across Canada <sup>25</sup>	3,105/ 3,138/ 3,171
• Without inhibitors (97%) <sup>25</sup>	3,012/ 3,044/ 3,075
Number of patients eligible for emicizumab (i.e., excluding Quebec)	2,332/ 2,357/ 2,381
<b>Market uptake (3 years)</b>	
Uptake (reference scenario)	See Source: Sponsor's pharmacoeconomic submission, BIA report, and model. <sup>8</sup>  Table 15 for patient proportions by severity and reference scenario treatment regimen.
Uptake (new drug scenario) <sup>a</sup>	

Parameter	Sponsor's estimate (reported as year 1, year 2, and year 3, if appropriate)
Adults:	[REDACTED]
• Severe, prophylaxis • Severe, on-demand • Moderate, prophylaxis, and on-demand <sup>a</sup> • Mild, prophylaxis, and on-demand	[REDACTED] [REDACTED] [REDACTED] [REDACTED]
Pediatrics:	[REDACTED]
• Severe, prophylaxis, and on-demand <sup>a</sup> • Moderate, prophylaxis, and on-demand <sup>a</sup> • Mild, prophylaxis, and on-demand	[REDACTED] [REDACTED] [REDACTED]
<b>Costs</b>	
Drugs <sup>b</sup> :	
• Emicizumab, cost per mg	\$122.0506
• Long-acting FVIII, cost per IU <sup>c</sup>	\$1.8900
• Short-acting FVIII, cost per IU <sup>d</sup>	\$1.1182
Annual treated bleeds, by product:	
• Emicizumab	1.7
• FVIII prophylaxis	1.9
• On-demand	40 (severe hemophilia); 10 (moderate hemophilia)

BIA = budget impact analysis; FVIII = factor VIII; IU = international unit.

<sup>a</sup> An additional 4% of all eligible non-inhibitor patients ( $4\% \times 2,333 = 86.63$  in year 1) were assumed to switch to emicizumab due to issues with venous access, regional access, or adherence/persistence. However, these patients were all assumed to be distributed across severe and moderate pediatric patients and moderate adult patients, regardless of whether they were receiving FVIII prophylaxis or on-demand therapy.

<sup>b</sup> Drug prices in the BIA were implemented per IU. To account for wastage, the sponsor assumed a wastage of 7%, 8%, and 6% for pediatric patients receiving emicizumab, long-acting FVIII, and short-acting FVIII, respectively. For adults, this was 4%, 4%, and 3%, respectively.<sup>8</sup>

<sup>c</sup> The ELOCATE cost was used to represent the price for all long-acting FVIII drugs.<sup>20</sup>

<sup>d</sup> The Nuwiq cost was used to represent the price for all short-acting FVIII drugs.<sup>20</sup>

Source: Sponsor's pharmacoeconomic submission, BIA report, and model.<sup>8</sup>

**Table 15: Sponsor's Estimations and Assumptions on Population Size, Disease Severity, and Treatment Regimen (Reference Scenario)**

	Age	Severity	Treatment	Approach to therapy	Patient numbers			
					Year 1	Year 2	Year 3	
Hemophilia A (without FVIII inhibitors)	Pediatric (< 12) 14%	Severe 60%	Long-acting FVIII 12%	Prophylaxis 95%	36	36	37	
				On-demand 5%	2	2	2	
		Moderate 10%	Short-acting FVIII 88%	Prophylaxis 95%	144	145	147	
				On-demand 5%	8	8	8	
	Adult (≥ 12) 86%	Severe 29%	Long-acting FVIII 12%	Prophylaxis 70%	5	5	5	
				On-demand 30%	1	1	1	
		Moderate 10%	Short-acting FVIII 88%	Prophylaxis 85%	21	21	22	
				On-demand 15%	4	4	4	
	Mild 31%	Long-acting FVIII 0%	Short-acting FVIII 100%	Prophylaxis 0%	0	0	0	
				On-demand 100%	0	0	0	
		Mild 61%		Prophylaxis 0%	0	0	0	
				On-demand 100%	97	98	99	
<b>Total number of patients eligible for emicizumab, per year</b>					<b>2,332</b>	<b>2,357</b>	<b>2,381</b>	

BIA = budget impact analysis; FVIII = factor VIII.

Note: Figures may not add up to 100% due to rounding.

<sup>a</sup> Proportion switching by year 3 indicates the proportion of patients in each severity and regimen category who are assumed to switch to emicizumab prophylaxis in the new drug scenario. See Table 14.Sources: Sponsor's pharmacoeconomic submission;<sup>8</sup> Budget Impact Analysis Report, Tables 1 and 2 and Figure 2; sponsor's submitted BIA model. Discrepancies between the sponsor's BIA report and model were corrected to reflect those reported in the model.

## Summary of the Sponsor's Budget Impact Analysis Results

Results of the sponsor's base case suggested an incremental cost of \$67,028,982 in year 1, \$70,861,365 in year 2, and \$81,247,668 in year 3, for a total incremental cost of \$219,138,016 over the 3-year time horizon when emicizumab is reimbursed for adult patients with severe hemophilia A (congenital FVIII deficiency) without FVIII inhibitors; for adult and pediatric patients with limited ability to receive regular IV therapy due to underlying factors, such as venous access challenges or geographical treatment access restrictions; or for adult and pediatric patients at significant risk for increased bleeding rates due to factors that lead to poor adherence or persistence.

## CADTH Appraisal of the Sponsor's BIA

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the results of the BIA:

- **Uncertainty in the cost of FVIII comparators.** The price of long- and short-acting FVIII was estimated by the sponsor from the PMPRB, which provides the maximum average potential price of a new patented medicine.<sup>20</sup> Public procurement of FVIII products is based on a tendering process in which the reimbursed price is likely to be lower.<sup>8</sup> Despite these prices being confidential, using the maximum price for the comparators introduces significant uncertainty because a higher comparator price will favour the adoption of emicizumab.
  - To address uncertainty in comparator pricing, CADTH conducted 2-way price-reduction analyses.
- **Uncertainty in annualized treated bleed rates for patients receiving on-demand therapy.** The sponsor estimated an ATBR of 40 for adult and pediatric patients with severe disease receiving on-demand therapy.<sup>26</sup> The clinical experts consulted by CADTH for this review noted that a patient would be unlikely to experience such a high frequency of bleeds without intervention.
  - In CADTH reanalyses, the ATBR for severe pediatric and adult patients was changed to 24.1, reflecting the on-demand values reported in patients with severe disease in the PROTEC VIII trial.<sup>27</sup>
- **Inappropriate adult weight used in the model.** The sponsor used an adult weight of 72.47 kg.<sup>4</sup> CADTH was unable to validate this weight in the cited publication. According to the clinical experts consulted by CADTH for this review, this weight may not be representative of Canadian adults; they noted that the average weight may be higher.
  - In CADTH reanalyses, the average weight among all patients in HAVEN 3 (79.1 kg) was used to inform the average weight of adults in the BIA.
- **Uncertainty regarding the uptake of emicizumab among eligible patients.** The BIA investigated the impact of the sponsor's reimbursement request, which included patients with both severe and non-severe disease who met specific criteria. In the sponsor's new drug scenario, a proportion of adults with severe disease who are currently receiving both prophylaxis and on-demand therapies were assumed to switch to emicizumab, whereas 0% of pediatric patients who have severe disease were assumed to switch. Separately, the sponsor assumed that █% of all patients eligible for emicizumab would switch to emicizumab, given that they would meet the specific sponsor's requested criteria. However, these patients were redistributed to the adult moderate population and pediatric severe and moderate populations only (Table 14). Estimates of market share are uncertain. Furthermore, this mathematical approach to deriving market share estimates is inconsistent and lacks transparency. The clinical experts consulted by CADTH for this review expected that uptake among adult patients with moderate disease would be similar to adult patients with severe disease. Experts also noted that adult patients receiving on-demand therapy may be less likely to switch to emicizumab than those treated with prophylaxis, which contradicts the sponsor's assumption that uptake among moderate patients would be equal across both treatment groups. Lastly, the CADTH clinical review report notes that the area of greatest unmet need is in the pediatric population. Therefore, uptake among pediatric patients may be higher than assumed in the sponsor's base-case analysis.
  - Given that uptake of emicizumab is highly uncertain, the impact of alternative uptake rates was explored in 2 scenario analyses.
- **Uncertainty in the proportion of patients across current FVIII treatment paradigms.** The sponsor estimated the proportions of patients, by age group and severity, who would be currently receiving FVIII prophylaxis versus on-demand therapy based, on clinical

expert opinion. These estimates are uncertain, given that the distribution of the current treatment mix is not publicly available. Because experts expect that adult patients currently receiving prophylaxis would be more likely to switch to emicizumab than those receiving on-demand therapy alone, these values in the reference scenario have the potential to influence the BIA results.

- CADTH was unable to address this limitation.
- **Comparator product missing.** According to the clinical experts consulted by CADTH for this review, some patients may use plasma-derived VWF products for treatment and prophylaxis of bleeds.<sup>28</sup>
  - CADTH was unable to address this limitation. Given that both the price and proportion of patients using VWF is unknown, so too is the direction and magnitude of the effect of their exclusion on the results of the BIA.

### CADTH Reanalyses of the Budget Impact Analysis

CADTH revised the sponsor's submission by changing the ATBR for on-demand patients with severe disease and adjusting the adult weight to align with the HAVEN 3 trial. Table 16 compares the assumption and values used by the sponsor with those used by CADTH in its reanalysis.

**Table 16: CADTH Revisions to the Submitted Budget Impact Analysis**

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
<b>Corrections to sponsor's base case (none)</b>		
<b>Changes to derive the CADTH base case</b>		
1. Uncertain ATBRs for on-demand patients	40	24.1
2. Inappropriate adult weight used in the model	72.47 kg	79.1 kg
CADTH base case		1 + 2

ATBR = annualized treated bleed rate.

The results of the CADTH step-wise reanalysis are presented in summary format in Table 17. A more detailed breakdown is presented in Table 18. Applying these changes increased the 3-year total budget impact to \$239,602,620.

**Table 17: Summary of the CADTH Reanalyses of the Budget Impact Analysis**

Stepped analysis	3-year total
Submitted base case	\$219,138,016
CADTH reanalysis 1: on-demand ATBR for patients with severe disease	\$220,610,606
CADTH reanalysis 2: adult patient weight	\$238,004,585
CADTH base case	\$239,602,620

ATBR = annualized bleed rate.

Note: The reanalyses are based on the sponsor's assumed prices for FVIII comparators. The true cost of these products is not publicly available.

CADTH also conducted additional scenario analyses to address remaining uncertainties:

1. Assume uptake among pediatric patients with severe disease will be equal to that of adults with severe disease, in addition to the █% uptake assumed by the sponsor (revised uptake among pediatric patients with severe disease = 40%, 45%, and 50% and 25%, 28%, and 30% for year 1, year 2, and year 3 for pediatric patients on prophylactic and on-demand treatment, respectively).
2. Revise uptake such that identical uptake rates were assumed by the approach to management, irrespective of hemophilia A severity and age:

	Year 1	Year 2	Year 3
Severe adult and pediatric, prophylaxis	█%	█%	█%
Moderate adult, prophylaxis			
Severe adult and pediatric, on-demand	█%	█%	█%
Moderate adult, on-demand			

3. Assume reimbursement in the population of adults with severe disease only (to align with the population studied in the HAVEN-3 trial and the target population modelled in the cost-effectiveness analysis).
4. Revise on-demand ATBR to reflect the sponsor's pharmacoeconomic submission (38.1).
5. Reduce the price of emicizumab to the value at which it would be cost-effective at a threshold of \$50,000 per QALY (89%).

The results of CADTH's scenario analyses demonstrate that the model is highly sensitive to comparator prices and the price of emicizumab. When the price of emicizumab was reduced by 89% (and FVIII comparator pricing remained unchanged), adopting emicizumab became cost-saving. Given that the true price of FVIII products is unknown, a 2-way price-reduction analysis between emicizumab and FVIII was conducted. The results are presented in Table 19.

**Table 18: Detailed Breakdown of the CADTH Reanalyses of the Budget Impact Analysis**

Stepped analysis	Scenario	Year 1	Year 2	Year 3	3-year total
<b>Submitted base case</b>	Reference	\$308,178,071	\$311,954,451	\$315,024,937	\$935,157,460
	New drug	\$375,207,054	\$382,815,816	\$396,272,606	\$1,154,295,476
	<b>Budget impact</b>	<b>\$67,028,982</b>	<b>\$70,861,365</b>	<b>\$81,247,668</b>	<b>\$219,138,016</b>
<b>CADTH base case</b>	Reference	\$327,837,313	\$331,951,020	\$335,194,972	\$994,983,305
	New drug	\$400,928,348	\$409,473,064	\$424,184,513	\$1,234,585,925
	<b>Budget impact</b>	<b>\$73,091,035</b>	<b>\$77,522,044</b>	<b>\$88,989,541</b>	<b>\$239,602,620</b>
<b>CADTH scenario analysis 1</b>	Reference	\$327,837,313	\$331,951,020	\$335,194,972	\$994,983,305
	New drug	\$404,589,328	\$413,602,923	\$429,198,783	\$1,247,391,034
	<b>Budget impact</b>	<b>\$76,752,015</b>	<b>\$81,651,903</b>	<b>\$94,003,811</b>	<b>\$252,407,729</b>
<b>CADTH scenario analysis 2</b>	Reference	\$327,837,313	\$331,951,020	\$335,194,972	\$994,983,305
	New drug	\$393,315,687	\$407,931,212	\$427,110,214	\$1,228,357,113
	<b>Budget impact</b>	<b>\$65,478,374</b>	<b>\$75,980,192</b>	<b>\$91,915,242</b>	<b>\$233,373,808</b>
<b>CADTH scenario analysis 3</b>	Reference	\$327,837,313	\$331,951,020	\$335,194,972	\$994,983,305
	New drug	\$374,418,227	\$385,785,421	\$400,271,159	\$1,160,474,808
	<b>Budget impact</b>	<b>\$46,580,914</b>	<b>\$53,834,401</b>	<b>\$65,076,188</b>	<b>\$165,491,503</b>

Stepped analysis	Scenario	Year 1	Year 2	Year 3	3-year total
CADTH scenario analysis 4	Reference	\$333,685,586	\$337,799,293	\$341,105,591	\$1,012,590,470
	New drug	\$406,461,763	\$414,835,325	\$429,488,926	\$1,250,786,015
	<b>Budget impact</b>	<b>\$72,776,177</b>	<b>\$77,036,032</b>	<b>\$88,383,335</b>	<b>\$238,195,545</b>
CADTH scenario analysis 5	Reference	\$327,837,313	\$331,951,020	\$335,194,972	\$994,983,305
	New drug	\$283,531,513	\$277,878,136	\$272,282,938	\$833,692,587
	<b>Budget impact</b>	<b>-\$44,305,801</b>	<b>-\$54,072,884</b>	<b>-\$62,912,033</b>	<b>-\$161,290,718</b>

ATBR = annualized bleed rate; BIA = budget impact analysis.

**Table 19: Two-Way Price-Reduction Analyses: 3-Year Total Budget Impact Analysis**

		Price of emicizumab				
		No reduction	25% reduction	50% reduction	75% reduction	90% reduction
Price of FVIII products	No reduction	\$239,602,620	\$126,992,131	\$14,381,643	-\$98,228,845	-\$165,795,138
	25% reduction	\$292,312,453	\$179,701,965	\$67,091,477	-\$45,519,012	-\$113,085,304
	50% reduction	\$345,022,286	\$232,411,798	\$119,801,310	-\$7,190,822	-\$60,375,471
	75% reduction	\$397,732,119	\$285,121,631	\$172,511,143	\$59,900,655	-\$7,665,638
	90% reduction	\$429,358,019	\$316,747,531	\$204,137,043	\$91,526,555	\$23,960,262

FVIII = factor VIII.

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