CADTH

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

ABR	annual bleeding rate
AE	adverse event
aPCC	activated prothrombin complex concentrate
BIA	budget impact analysis
BPA	bypassing agent
CBA	Canadian Blood Services
CUA	cost-utility analysis
FEIBA	factor eight inhibitor bypassing activity
FVIII	factor VIII
ICUR	incremental cost-utility ratio
ITI	immune tolerance induction
NIS	non-interventional study
PMPRB	Patented Medicine Prices Review Board
QALY	quality-adjusted life-year
rFVIIa	recombinant factor VIIa
SMR	standardized mortality ratio

Drug	Emicizumab (Hemlibra)
Indication	Indicated for hemophilia A (congenital factor VIII deficiency) patients with factor VIII inhibitors as routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes
Reimbursement Request	As per indication
Dosage Forms	30 mg/mL, 60 mg/0.4mL, 105 mg/0.7mL, 150 mg/1mL solution in single-use vials
NOC Date	August 2, 2018
Manufacturer	Hoffman-La Roche Limited

Executive Summary

Background

Emicizumab is a recombinant, humanized, bispecific, therapeutic monoclonal antibody designed to replace the hemostatic function of factor VIIIa in the human body by bridging activated factor IX and factor X. It is indicated for the treatment of patients with hemophilia A (congenital factor (F)VIII deficiency) with FVIII inhibitors for routine prophylaxis to prevent or reduce the frequency of bleeding episodes. It is administered by subcutaneous injection and is available in several single-use vial sizes: 30 mg/1 mL, 60 mg/0.4 mL, 105 mg/0.7 mL and 150 mg/1 mL. The recommended use is 3 mg/kg once weekly for four weeks, followed by 1.5 mg/kg weekly as long-term prophylaxis.[1] The manufacturer submitted a unit cost of $[redacted].[2] Based on an average patient's weight of 70 kg and a loading dose of 3.0 mg/kg for the first four weeks followed by maintenance doses of 1.5 mg/kg, CADTH estimated the annual cost per patient to be $[redacted] in the first year, and $[redacted] in all subsequent years. This calculation assumes no drug wastage.

This report is based on a critical appraisal of economic information provided by the manufacturer, which consisted of an economic evaluation and a budget impact analysis (BIA).[2] CADTH conducted reanalyses to consider alternative assumptions and inputs where relevant and possible.

Economic Evaluation

The manufacturer submitted a cost-utility analysis comparing the following treatments for hemophilia A with FVIII inhibitors: prophylaxis with emicizumab; prophylaxis with bypassing agents (BPAs); and on-demand (episodic) use of BPAs.[2] The BPA therapy (i.e., prophylaxis and on-demand) consisted of the following two drugs (assumed to be used in proportion to their market shares in Canada): Factor Eight Inhibitor Bypassing Activity (FEIBA), which is an activated prothrombin complex concentrate; and, Niastase (recombinant activated human FVIIa, recombinant FVIIa). The analysis was conducted from the Canadian public payer perspective over a lifetime horizon to a maximum age of 100 years. The manufacturer's Markov model was based on two health states: alive with hemophilia A with inhibitors (and receiving one of the three previously mentioned therapies); and dead. All patients in the model started in the alive state and could experience bleeding events or death during a model cycle (the risk of these events depended on the treatment received). The model cycle length was one year, with patients starting in the model at 20 years of age. Both outcomes

and costs accrued beyond the first year of the model were discounted at a rate of 1.5%, per CADTH guidelines.[3]

The model population, treatment response, and adverse event (AE) rates were based on two studies: HAVEN 1 (a 24-week phase III randomized controlled trial, including adults and adolescents, comparing emicizumab prophylaxis with on-demand treatment with BPAs), and a single-arm, non-interventional study (NIS) of BPA prophylaxis. The number of bleeding events reported in these studies was used to estimate annual bleeding rate for each therapy (prophylaxis and on-demand), which were then applied to the alive health state in the model. As such, health events (such as bleeding and arthroplasty), and their impact on quality of life (utility), were not explicitly defined as health states in the model.

The manufacturer reported that emicizumab prophylaxis dominated BPA prophylaxis; i.e., emicizumab was associated with lower total costs and higher quality-adjusted life-years (QALYs). However, compared with on-demand BPAs, emicizumab was associated with greater QALYs (8.980) at an additional cost of $12,760,415, resulting in an incremental cost-utility ratio (ICUR) of $1,420,982 per QALY. The manufacturer conducted a scenario analysis with a starting age of zero to include pediatric population. In this scenario, emicizumab dominated BPA prophylaxis; however, for the comparison against on-demand BPA, emicizumab was associated with 8.882 additional QALYs and a $11,976,886 higher cost, resulting in an ICUR of $1,348,371 per QALY.

Several key limitations were identified by CADTH with the manufacturer's economic model. First, the economic analysis was based on an unconventional two-state model (i.e., alive and dead), and all bleeding-related events were absorbed within the alive health state. The manufacturer assumed constant treatment-specific utility values for the alive health state in the model. Using this modelling approach (which is not based on health events and disease states), it is not possible to establish what is causing differences in utility values between treatment groups. Estimated QALYs may be incorrect because utility values are based on a single fitted utility at the end of the follow-up period for each treatment group — this does not take account of variation in quality of life during the follow-up. Furthermore, the cumulative effect of bleeding events (such as arthropathy) was not clearly reflected in the economic model. Second, the manufacturer used an unpublished, observational, single-arm, NIS to estimate bleeding rate and quality of life in patients receiving BPA prophylaxis. This non-randomized evidence is used alongside and directly compared with randomized trial data for emicizumab prophylaxis and on-demand BPA (HAVEN 1 study). Because key model parameters for the three treatment groups were based on two different data sources and study designs (NIS and randomized controlled trial), CADTH noted inconsistency in the relationship between bleeding rates and utility values in the three treatment groups; i.e., patients on BPA prophylaxis (in the NIS) had, on average, a lower bleeding rate but also had lower average utility value compared with on-demand BPA patients in the HAVEN 1 trial. Furthermore, the manufacturer assumed that patients receiving on-demand BPA would require an arthroplasty every 15 years (with a total of four arthroplasties throughout their lifetime) but patients on prophylactic emicizumab or BPAs were assumed to not require any arthroplasty; however, no evidence was provided to support this assumption. Moreover, the manufacturer assumed a utility value of zero for one month for patients undergoing arthroplasty — this assumption is also not supported by evidence or by the clinical expert consulted by CADTH. Finally, the manufacturer assumed higher mortality risk for patients receiving on-demand BPA compared with patients on prophylaxis. While the clinical expert consulted by CADTH considered this assumption to be plausible, no evidence was provided by the manufacturer to support this assumption.

CADTH reanalyses could not address the first and most important limitation previously described; i.e., the inappropriate modelling approach that introduced significant uncertainty into the analysis. However, CADTH reanalyses addressed the following other limitations:

- Instead of using the lower-quality NIS, the annual bleeding rate for BPA prophylaxis was estimated by applying the relative bleeding risk compared with on-demand BPA, as reported in a published study (Antunes et al.).[4] This study was identified by the manufacturer in a systematic review and has been used in a sensitivity analysis in the manufacturer's submission.
- Patients on on-demand BPA treatment were assumed to experience a maximum of two arthroplasties, at the age of 40 and 55, based on consultation with CADTH's clinical expert. The assumption that patients on prophylaxis do not require any arthroplasty was considered reasonable.
- The quality-of-life impact of arthroplasty was modelled by applying arthroplasty-related disutility of –0.39 for one month. This is based on a study of knee arthroplasty in patients with hemophilia A with inhibitors.[5]

In the CADTH base-case and scenario analyses, emicizumab compared with BPA prophylaxis remained a dominant strategy (i.e., emicizumab was associated with lower total costs and higher QALYs). However, compared with on-demand BPAs, emicizumab was associated with an ICUR of $1,442,642 per QALY gained. A price reduction of approximately 42% would be required for emicizumab to be cost-effective compared with on-demand BPA strategy at a willingness to pay of $50,000 per QALY. In scenario analyses, emicizumab had the highest ICUR, $2,000,271, when a 30% lower body weight was assumed, and lowest ICUR, $1,364,195, when the treatment was assumed to start at the age of zero when compared with on-demand BPAs. In all scenarios, emicizumab was dominant over BPA prophylaxis.

The manufacturer's submission did not assess the cost-effectiveness of emicizumab in the non-inhibitor population, although the budget impact of extending access to the non-inhibitor population was explored (see next section). CADTH noted that the manufacturer has conducted two studies (HAVEN 3 and HAVEN 4) comparing emicizumab with no prophylaxis in the non-inhibitor population.[6,7] HAVEN 3 has a similar study design as HAVEN 1 (HAVEN 4 is a non-randomized, single-arm observational study). Given that the manufacturer did not use the evidence from these studies in the economic evaluation, its impact on the ICUR is unclear.

Budget Impact

The manufacturer conducted a BIA to assess the national budgetary implications of reimbursing emicizumab in Canada (Quebec was excluded from the analysis).[2] A prevalence-based approach was taken using a three-year analysis time frame; reference year: 2018, year 1: 2019, year 2: 2020, year 3: 2021. The manufacturer considered the full indicated population (children and adults with hemophilia A with inhibitors) and conducted a scenario analysis to assess impact of the potential use in a non-inhibitor population. The submitted BIA analysis was developed in Microsoft Excel and compared two budget scenarios: a reference scenario, where patients were treated with BPAs (either prophylactically or on-demand) or FVIII (high-dose or immune tolerance induction); and a new treatment scenario, where patients currently on BPAs (prophylactic or on-demand) may switch to prophylactic emicizumab. The total cost for each scenario was calculated based on the estimated number of patients likely to receive each treatment multiplied by the per-

patient costs associated with the treatment, including both the drug acquisition cost (based on dosage and unit cost) and treatment-related health system costs (i.e., hospitalization cost and AE management cost). The budget impact was then calculated by subtracting the total cost of the reference scenario from the total cost of the new treatment scenario.

To determine the number of patients likely to receive BPAs or emicizumab, the manufacturer used the total number of patients with hemophilia A (as estimated using Statistics Canada estimates),[8,9] and assumed that 3% of these patients have FVIII inhibitors.[10] These patients were assumed to receive BPAs (FEIBA or Niastase) in proportion based on their market shares (see Figure 2). Patients currently on FVIII treatment (i.e., high-dose FVIII or immune tolerance induction) were assumed to continue on these drugs (in the base case). For the new treatment scenario, the manufacturer assumed that [redacted] of pediatric patients and [redacted], [redacted] and [redacted] of adult patients who are currently on prophylactic BPA would switch to emicizumab in tears 1, 2, and 3, respectively. Of the patients currently receiving on-demand BPAs, the uptake rate of emicizumab was assumed to be [redacted], [redacted], and [redacted] in years 1, 2, and 3, respectively.

The manufacturer estimated the following cost savings associated with treating hemophilia A with inhibitors with emicizumab: $31,295,993 in year 1, $40,705,147 in year 2, and $48,991,658 in year 3. Cost savings were due to the lower drug price of emicizumab prophylaxis compared with BPA prophylaxis. A scenario analysis excluding non-drug medical costs (i.e., only including drug acquisition costs) resulted in cost savings of $30,928,588 in year 1, $40,229,306 in year 2, and $48,342,943 in year 3. The manufacturer included an additional scenario extending the use of emicizumab to the non-inhibitor population. The non-inhibitor population was categorized based on severity of hemophilia: patients with moderate or severe hemophilia were assumed to receive one of two treatments: long-acting or short-acting FVIII (either prophylactically or on-demand) in proportion to their market shares, whereas patients with mild hemophilia received only short-acting FVIII (see Figure 3). The manufacturer reported that emicizumab would result in an increase in budgetary costs by $60,549,175 in year 1, $68,316,619 in year 2, and $85,527,770 in year 3. A scenario analysis, excluding non-drug medical costs (i.e., including drug acquisition costs only) resulted in an increase in budgetary cost by $63,950,098 in year 1, $72,586,379 in year 2, and $90,826,076 in year 3. Finally, aggregating the costs for patients with hemophilia A with and without inhibitors resulted in a total cost increase of $29,253,183 in year 1, $27,611,472 in year 2, and $36,536,112 in year 3.

CADTH identified several sources of uncertainty and potential limitations relating to the BIA submission. First, the manufacturer's BIA used an annual bleeding rate of 18.6 for on-demand adult patients; however, in HAVEN 1, the value was reported as 23.3,[11] which was also used in the cost-utility analysis. This correct value was used in CADTH reanalysis. Second, the average patient weight in the BIA (for dose calculation) was based on Australian patients (pediatric weight = [redacted]; adult weight = [redacted]);[12] however, it is unclear how this compares with body weights of the Canadian patients. CADTH reanalysis conducted sensitivity analyses to assess the impact of using lower body weight. Third, the manufacturer considered a low uptake rate of emicizumab in the on-demand population (i.e., [redacted] in years 1 to 3, respectively) and a modest uptake in the adult population on BPA prophylaxis ([redacted] in years 1 to 3, respectively). Based on consultations with Canadian Blood Services (CBS) and CADTH's clinical expert, CADTH reanalysis assumed that emicizumab is expected to be adopted by 100% of patients on BPA prophylaxis and on-demand BPA from year 1. Finally, CADTH reanalysis used revised BPA unit costs based on CBS data, and also used a more recent population prevalence of hemophilia. Based on

2017 estimates obtained from the Canadian Hemophilia Registry, there were 372 pediatric and 2,426 adult patients with hemophilia A in Canada, with 2.9% (81 patients) with FVIII inhibitors (27 pediatric and 54 adults).[13]

CADTH reanalysis estimated the following budget impact associated with treating hemophilia A with inhibitors with emicizumab: cost savings of $32,920,731 in year 1, $34,750,021 in year 2, and $36,545,226 in year 3. When excluding non-drug–related costs (i.e., hospitalization and AE costs), CADTH base-case reanalysis estimated cost savings of $32,253,708 in year 1, $34,082,997 in year 2, and $35,853,064 in year 3. Based on CADTH's sensitivity analysis, results were most sensitive to body weight (budget impact in year 1 ranged from cost savings of $23,228,991 when body weight was reduced by 30% to savings of $42,596,844 when body weight was increased by 30% of base case).

CADTH reanalysis of the non-inhibitor population included the following changes to the manufacturer's submission: 2017 figures (from the most recent Canadian Hemophilia Registry report) for the number of patients with hemophilia A without inhibitors, stratified by severity; and FVIII revised market shares and FVIII unit costs (based on CBS data). This analysis estimated a budget increase of $76,431,845 in year 1, $90,122,437 in year 2, and $110,764,370 in year 3. When excluding non-drug–related costs (i.e., hospitalization and AE costs), CADTH reanalysis in the non-inhibitor population estimated an increase cost of $78,793,929 in year 1, $93,062,975 in year 2, and $114,346,925 in year 3. The primary reasons for the difference between the manufacturer's and CADTH's budget impact estimates were the assumed proportion of patients who would receive emicizumab, and the assumed unit cost of short- and long-acting FVIII.

CADTH reanalysis estimated that the net cost of reimbursing emicizumab in the full population of patients with hemophilia A in Canada, including those with or without inhibitors, is expected to be $43,511,114 in year 1, $55,372,417 in year 2, and $74,219,144 in year 3. When excluding non-drug–related costs, CADTH estimated the net cost to be $46,540,221 in year 1, $58,979,978 in year 2, and $78,493,861 in year 3.

Conclusions

The manufacturer evaluated the cost-effectiveness and budget impact of emicizumab prophylaxis in patients with hemophilia A with inhibitors. In the inhibitor population, emicizumab is the dominant treatment compared with BPA prophylaxis, but, compared with on-demand BPA, emicizumab would require a price reduction 42% to be cost-effective at a conventionally accepted willingness-to-pay threshold of $50,000. The cost-effectiveness of emicizumab in the non-inhibitor population remains unknown. CADTH estimated that reimbursing emicizumab for patients with hemophilia A with inhibitors will result in cost savings, but reimbursing it in both inhibitor and non-inhibitor populations would result in an increased cost of $78,493,861 (in year 3) when considering only drug costs. CADTH noted that there is paucity of evidence, both on efficacy and utilization of drugs considered in this report; therefore, the results should be interpreted with consideration of the assumptions outlined in the previously described analyses.

Information on the Economic Submission

Manufacturer's Economic Evaluation

The manufacturer submitted a cost-utility analysis (CUA) comparing the following treatments for hemophilia A with factor (f)VIII inhibitors: prophylaxis with emicizumab; prophylaxis with bypassing agents (BPA); and on-demand (episodic) use of BPAs.[2] The BPA treatment groups (i.e., prophylaxis and on-demand) consisted of the following two drugs (assumed to be used in proportion to their market shares in Canada): Factor Eight Inhibitor Bypassing Activity (FEIBA), which is an activated prothrombin complex concentrate (aPCC); and Niastase (recombinant activated human FVIIa, recombinant [r]FVIIa). Eighty per cent and 20% of the patients on prophylaxis were assumed to be treated with FEIBA and Niastase, respectively; whereas, 30% and 70% of the patients on on-demand treatment were assumed to be treated with FEIBA and Niastase, respectively. The analysis was conducted from the Canadian public payer perspective over a lifetime horizon to a maximum age of 100 years. Manufacturer developed a Markov model based on the following two health states: alive with hemophilia A with inhibitors (and receiving one of the three previously mentioned treatments); and dead. The model cycle length was one year, with patients starting in the model at 20 years of age. All patients in the model started in the alive state and could experience bleeding events or death during a model cycle (the risk of these events depended on the treatment being received). Costs and outcomes were discounted at 1.5%, per CADTH guidelines.[3] Results were based on probabilistic sensitivity analysis using 5,000 iterations.

The characteristics of the model population, rates of treatment response, and adverse event (AE) rates were based on two studies: HAVEN 1 — a phase III randomized controlled trial in adults and adolescents (≥ 12 years old) comparing the efficacy, quality of life, and safety of emicizumab prophylaxis with on-demand treatment with BPAs; and a single-arm, non-interventional study (NIS) evaluating bleeding incidence, quality of life, and safety in patients with hemophilia A with inhibitors receiving BPA prophylaxis. The number of bleeding events reported in these studies was used to estimate the annual bleeding rate (ABR) for each therapy (prophylaxis and on-demand), which were then applied to the alive health state in the model. As such, health events (such as bleeding and arthroplasty) and their impact on quality of life (utility), were absorbed within the alive health state and not explicitly defined as health states in the model. Using this modelling approach, the manufacturer applied treatment-specific utility values for the alive health states in the model. The emicizumab prophylaxis group had an ABR of 2.9 compared with the on-demand BPA group's ABR of 23.3; i.e., emicizumab prophylaxis was associated with an 87% reduction in treated bleeding rate compared with on-demand BPA. For the BPA prophylaxis group, the ABR was based on the observed bleeding rate in the NIS (ABR = 14.9). These ABR values were used in the economic model. The model assumes that all bleeding episodes were treated with BPAs across all groups.

The manufacturer's submission also included a systematic review to identify randomized clinical trials comparing BPA prophylaxis with on-demand BPA for mild, moderate, and severe hemophilia A with inhibitors. Four studies[4,11,14,15] were identified but not pooled due to clinical heterogeneity. The Antunes et al. (2014) study was deemed the most relevant due to its similarity in design to the HAVEN 1 study. This study was used in a sensitivity analysis that estimated the ABR for BPA prophylaxis by applying the relative risk in Antunes et al.

(2014) to the on-demand ABR in HAVEN 1 — this estimate was used in place of the ABR in the NIS.

The probability of death was informed by the standardized mortality rate (SMR) in patients with hemophilia A, as reported in the literature,[16] and was based on disease severity (i.e., mild to moderate, or severe). This SMR was applied to the background age-specific Canadian mortality rate.[9] The manufacturer assumed that patients treated with on-demand BPA will have severe hemophilia, whereas patients on emicizumab or BPA prophylaxis will have mild-to-moderately severe hemophilia. The SMR for patients with mild-to-moderate hemophilia (SMR = 1.19) was used for patients receiving prophylaxis; while the SMR for patients with severe hemophilia (SMR = 2.69) was applied to patients under on-demand BPA treatment.

The manufacturer used an unconventional modelling approach that included only two health states, alive and death, and all disease-related events (such as bleeding and arthroplasty) were absorbed within the alive health state. Utility value for BPA prophylaxis was based on the NIS data; a piecewise linear mixed model was fitted to estimate the utility level at the end of the NIS study. In short, for all three treatment groups, the utility value for the alive state was based on regression-based fitted value at the end of follow-up (i.e., HAVEN 1 or NIS). The length of the NIS was not reported by the manufacturer.

Patients on on-demand BPA treatment were assumed to undergo arthroplasty every 15 years; however, patients on emicizumab or BPA prophylaxis were assumed to not require arthroplasty due to lower bleeding risk. Patients undergoing arthroplasty were assumed to experience a disutility of –0.65 for one month; the resulting utility value for patients receiving arthroplasty was equal to zero for one month.

Drug dose was calculated using UK-based age-specific body weight ranging from [redacted]. A constant body weight of [redacted] was assumed for all patients over 18 years old. The starting age in the model is 20 years and was estimated as the median age of patients in the Canadian Hemophilia Registry.[10] For BPA prophylaxis and on-demand treatment, the manufacturer assumed that unused product from a vial can be used for another patient; however, given that any unused emicizumab product left in the vial needs to be discarded, vial sharing is not feasible with emicizumab and patients were assumed to be treated with the nearest vial size to minimize wastage. Drug costs were based on the manufacturer's submitted price[2] and the New Patented Medicines Reported to the Patented Medicine Prices Review Board (PMPRB).[17] The model does not include the cost of physician visits, monitoring, nursing, physiotherapy, and central venous access devices placement and treatment of infections. Hospitalization costs to treat bleeding events were obtained from the Ontario Case Costing Initiative.[18] The number of hospitalization days was assumed to be the same for all bleeding events. The cost of arthroplasty was obtained from the Canadian Institute for Health Information,[19] and the manufacturer assumed that a repeat arthroplasty would be required every 15 years at ages 25, 40, 55, and 70.

Emicizumab is likely to be used in patients without inhibitors. CADTH noted that the manufacturer has conducted two studies (HAVEN 3 and HAVEN 4) comparing emicizumab with no prophylaxis;[6,7] however, these studies have methodological limitations, i.e., HAVEN 4 is a non-randomized, single-arm observational study, whereas HAVEN 3 uses an unpublished, observational, single-arm NIS to estimate bleeding rate and quality of life in patients receiving BPA prophylaxis. These studies provide low-quality evidence that cannot be appropriately used in an economic evaluation. CADTH is unable to comment on the cost-effectiveness of emicizumab in this population given that the manufacturer CUA submission

is only applicable to a population of patients with hemophilia A with FVIII inhibitors who will not be treated with immune tolerance induction (ITI) or for whom ITI has been unsuccessful.

Manufacturer's Base Case

In the manufacturer's base case (probabilistic) analysis, compared with on-demand treatment with BPA, emicizumab was associated with 8.980 additional quality-adjusted life-years (QALYs) and a $12,760,415 higher cost. The incremental cost-utility ratio (ICUR) for emicizumab versus on-demand treatment with BPA was $1,420,982 per QALY (Table 1). Emicizumab prophylaxis dominated BPA prophylaxis; i.e., emicizumab was associated with lower total costs and higher QALYs.

Table 1: Results of the Manufacturer's Base Case (Probabilistic)

	Emicizumab	BPA Prophylaxis	BPA On-Demand	Incremental Difference (Emicizumab vs. BPA Prophylaxis)	Incremental Difference (Emicizumab vs. BPA On-Demand)
Total costs ($)	32,574,676	88,227,298	19,814,261	–55,652,622	12,760,415
Total QALYs	31.476	24.078	22.496	7.397	8.980
ICUR ($/QALY)				Dominates	1,420,982

BPA = bypass agent; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; vs. = versus.

Source: Manufacturer's submission.[2]

There was a calculation error in the manufacturer's model. In the first cycle arthroplasty costs for the on-demand group were set to zero. This error was addressed, and the updated model was used in CADTH's reanalysis (Table 2).

Summary of Manufacturer's Sensitivity Analyses

Probabilistic scenario analyses were conducted that varied model parameters and assumptions and included the following: body weight (UK-based ±20% by age); alternative annual bleed rates (clinical trial ABRs ±20%, as well as alternative ABR derived from indirect treatment comparison); AEs estimated from the literature instead of clinical trials; undiscounted costs and QALYs; alternative arthroplasty, hospitalization, and AE costs; no disutility associated with arthroplasties; alternative mortality rates; and decreasing the time horizon to 40 and 60 years (Table 15).

The results of scenario analyses showed that the model results were most sensitive to the following parameters and assumptions:

- Assuming alternate utility values based on clinical trial data ±20%: ICUR for emicizumab versus on-demand treatment with BPAs increased to $1,775,362 when decreasing clinical trial utilities by 20%. It decreased to $1,190,373 when increasing clinical trial utilities by 20%.
- Assuming alternate annual bleeding rates based on clinical trial data ±20% for all comparators: ICUR for emicizumab versus on-demand treatment with BPAs increased to $1,794,198 when decreasing clinical trial ABR by 20%. It decreased to $1,058,008 when increasing clinical trial ABR by 20%.
- Assuming alternate body weight: The manufacturer-reported ICUR for emicizumab versus on-demand treatment with BPAs decreased to –$18,051 when reducing UK-

based weight by 20%. It decreased to –$57,504 when increasing UK-based weight by 20%. However, this value could not be replicated. CADTH found that reducing UK-based weight by 20% increased the ICUR to $1,790,007, and increasing it by 20% reduced the ICUR to $1,054,810.

The manufacturer conducted a scenario analysis with a starting age of zero to include pediatric population. In this scenario, emicizumab dominated BPA prophylaxis; however, for the comparison against on-demand BPA, emicizumab was associated with 8.882 additional QALYs and a $11,976,886 higher cost, resulting in an ICUR of $1,348,371 per QALY.

In all scenario analyses emicizumab was a dominant strategy compared with BPA prophylaxis.

Cost-effectiveness acceptability curves based on probabilistic sensitivity analyses showed that on-demand treatment had a high chance (> 99%) of being cost-effective over prophylaxis with emicizumab or BPAs for thresholds up to $100,000.

Limitations Identified With the Manufacturer's Economic Submission

CADTH identified the following limitations in the manufacturer's model.

Model structure: The manufacturer used an unconventional modelling approach that included only two health states, alive and dead. Disease-related events (such as bleeding and arthroplasty), and their impact on quality of life (utility), were absorbed within the alive health state and were not explicitly defined as health states in the model. Using this modelling approach, it is not possible to establish what is causing differences in utility values between treatment groups. Moreover, it can potentially incorrectly estimate quality-of-life values because it is based on a single fitted utility value at the end of the follow-up period for each treatment group — this does not take account of variation in quality of life during the follow-up. The use of treatment-specific utilities is discouraged as the more transparent approach is to assign utility values to clinically relevant health states, per CADTH guidelines.[3] Furthermore, the cumulative effect of bleeding events (such as arthropathy) was not reflected in the model. Finally, the dynamic change in inhibitor profile in the pediatric population (i.e., patients with pediatric hemophilia A receiving emicizumab that go on to not develop inhibitors) was not included in the manufacturer's submission. Given the design of the model, it was not possible to address these structural limitations.

Estimate of relative treatment effect: There is lack of head-to-head randomized evidence comparing emicizumab prophylaxis with BPAs prophylaxis. The manufacturer used an unpublished, observational, single-arm, NIS to estimate bleeding rates in patients receiving BPA prophylaxis. This lower-quality, non-randomized evidence is used alongside and directly compared with randomized trial data for emicizumab prophylaxis and on-demand BPA (HAVEN 1 study). The manufacturer also conducted a systematic review and identified one study[4] comparing BPA prophylaxis with on-demand BPA; however, this study was only used in a sensitivity analysis.

Mortality: The manufacturer assumed that patients receiving on-demand BPA experience an SMR of severe hemophilia A throughout their lifetime, whereas patients receiving emicizumab or BPA prophylaxis experience SMR of mild-to-moderate hemophilia A. While the clinical expert consulted by CADTH considered this mortality benefit of prophylaxis to be plausible, it was noted that no evidence was provided by the manufacturer to support this

assumption. CADTH reanalysis explored the impact of this assumption by assuming no treatment-attributable mortality benefit in a scenario analysis.

Arthroplasty assumptions: The manufacturer assumed that patients on prophylactic emicizumab or BPA would not require an arthroplasty due to reduced risk of bleeding, whereas patients receiving on-demand BPA would require an arthroplasty every 15 years (at ages 25, 40, 55, and 70, resulting in four arthroplasties throughout their lifetime). The clinical expert suggested that an average patient is expected to undergo two arthroplasties during their lifetime. The assumption that patients on prophylaxis do not require any arthroplasties is consistent with the opinion of the clinical expert consulted by CADTH.

For quality-of-life impact of arthroplasties, the manufacturer assumed zero utility for one month; however, CADTH reanalysis used a disutility value of –0.39 for one month based on the literature.[20]

Treatment of AEs: The manufacturer assumed that 30% of treated bleeds would be treated with FEIBA for patients on emicizumab prophylaxis. Concomitant use of emicizumab prophylaxis with an activated prothrombin complex concentrate (such as FEIBA) to treat episodic bleeds is associated with thrombotic microangiopathy and thromboembolism risk when a cumulative amount of > 100 U/kg per 24 hours aPCC was administered for 24 hours or more. According to the clinical expert consulted by CADTH, physicians may therefore choose Niastase over FEIBA to treat bleeds for patients on emicizumab prophylaxis. Treatment with Niastase is associated with higher costs due to increased dose compared with FEIBA; therefore, the assumption that a proportion of the bleeds were treated with FEIBA, instead of Niastase, decreased the costs associated with emicizumab treatment. CADTH explored the impact of this assumption in a scenario reanalysis by assuming that 100% of bleeds in patients receiving emicizumab prophylaxis would be treated with Niastase.

Costs: Several cost items were not included in the manufacturer's analysis, including physician visit, monitoring for neutralizing antibodies, nurse visits, and central venous access devices placement and the cost of treating infections. While some of these items are relatively low in cost, not including the cost of monitoring of neutralizing antibodies for patients receiving emicizumab and the cost of equipment required to administer emicizumab is likely to underestimate the total cost associated with emicizumab treatment. The cost of emicizumab administration was not available and is likely to vary between centres. Based on feedback from Canadian Blood Services (CBS), an assay to detect neutralizing antibodies is currently being developed and will serve as a Canadian reference. However, the clinical usefulness of an emicizumab-specific anti-drug antibodies assay is uncertain, and the cost associated with monitoring for neutralizing antibodies could not be estimated due to lack of data. Due to lack of information in the manufacturer's submission, the cost of adopting emicizumab as a new technology, including the cost of training professionals to deliver treatment, patient counselling, and any additional laboratory testing for monitoring patients was not included in CADTH reanalysis. Hence, the cost estimates should be interpreted with consideration of this limitation.

Treatment discontinuation: The manufacturer assumed adherence to be 100% for both emicizumab and BPA prophylaxis, which is unlikely according to CADTH's clinical expert. Previous evidence has shown that adherence to BPA prophylaxis in patients without inhibitors is likely to be between 26% and 96%.[21] Higher assumed adherence may overestimate the effectiveness of prophylaxis compared with on-demand treatment.

Short follow-up: The economic model, and the predicted costs and benefits of treatments, is based on a lifetime horizon, but the evidence from HAVEN 1 and NIS were conducted over a shorter follow-up period (i.e., the median exposure to emicizumab in the HAVEN 1 clinical trial was 24 weeks; range: 3 to 47.9 weeks). This follow-up was not sufficiently long to make assumptions around the use of emicizumab prophylaxis, or to demonstrate the safety of concomitant use of emicizumab prophylaxis with BPAs to treat bleeding events over a patient's lifetime.

CADTH Reanalyses

CADTH reanalyses could not address the first and most important limitation described; i.e., the inappropriate modelling approach that introduced significant uncertainty into the analysis. However, CADTH reanalyses addressed the following other limitations:

1. Instead of using the lower-quality NIS, the annual bleeding rate for BPA prophylaxis was estimated by applying the relative bleeding risk compared with on-demand BPA, as reported in a published study (Antunes et al.).[4] This study was identified in the manufacturer's systematic review and was also used the manufacturer's sensitivity analysis.
2. Patients on on-demand BPA treatment are assumed to experience two arthroplasties throughout their lifetime, at ages 40 and 55.
3. The quality-of-life impact of arthroplasty was modelled by applying arthroplasty-related disutility of –0.39 for one month. This is based on the published disutility value of knee arthroplasty for hemophilia patients with inhibitors,[5] which was felt to be more realistic.
4. CADTH base case (1 to 3).

Scenario analyses using the CADTH base case:

4a: CADTH base case plus all bleeding events for patients on emicizumab prophylaxis were assumed to be treated with rFVIIa.

4b: CADTH base case plus all patients were assumed to undergo arthroplasty every 15 years regardless of treatment.

4c: CADTH base case plus BPA dose for treating bleeding events was assumed to be the same for all treatment groups (i.e., aPCC and rFVIIa dose of 132 IU/kg and 296 mcg/kg, respectively).

4d: CADTH base case plus body weight of patients was assumed to be 30% less than the base case (this is equal to 53 kg).

4e: CADTH base case plus assuming a starting age of zero to include the pediatric population.

4f: CADTH base case plus assuming no treatment-attributable reduction in mortality. All patients experience an SMR of severe hemophilia regardless of treatment.

The results of CADTH reanalyses are presented in Table 2. In CADTH base-case analysis, compared with on-demand treatment with BPA, emicizumab was associated with 8.873 additional QALYs and a $12,800,583 higher cost. The ICUR for emicizumab was $1,442,642 per QALY when compared with on-demand treatment with BPAs. Emicizumab was consistently the dominant strategy compared with BPA prophylaxis across all scenarios; i.e., it was less costly and more effective than BPA prophylaxis. The change that most heavily impacted the ICUR was the assumption that patients undergoing an arthroplasty experience a disutility of –0.39 (analysis 3; ICUR: $1,434,000 per QALY).

The results of scenario analyses showed that the model results were most sensitive to reducing body weight by 30% less than base case (the ICUR increased to $2,000,271 per QALY), assuming no treatment-attributable reduction in mortality (the ICUR increased to $1,679,480), and reducing the starting age to zero to include the pediatric population (the ICUR decreased to $1,364,195 per QALY).

Table 2: Results From CADTH Reanalyses (Probabilistic)

	Description	Emicizumab vs. BPA On-demand			Emicizumab vs. BPA Prophylaxis		
		Incremental Cost ($)	Incremental QALYs	ICUR ($/QALY)	Incremental Cost ($)	Incremental QALYs	ICUR ($/QALY)
Manufacturer Base Case		**12,760,415**	**8.980**	**1,420,982**	**–55,652,622**	**7.397**	Dominates
	Corrected manufacturer base case[a]	12,791,706	8.966	1,426,754	–55,660,226	7.385	Dominates
1	Relative risk of annual bleeding rate for BPA prophylaxis based on manufacturer's systematic review	12,789,240	8.962	1,427,092	–49,392,214	7.366	Dominates
2	Patients on on-demand BPA experience 2 arthroplasties throughout their life	12,768,895	8.914	1,432,496	–55,664,293	7.399	Dominates
3	Arthroplasty-related disutility of –0.39	12,792,420	8.921	1,434,000	–55,662,874	7.391	Dominates
4	**CADTH base case (1 to 3)**	**12,800,583**	**8.873**	**1,442,642**	**–49,403,244**	**7.384**	**Dominates**
Scenario Analyses of CADTH Base Case							
4a	All bleeding events for patients on emicizumab prophylaxis treated with rFVIIa	13,077,609	8.891	1,470,894	–49,106,703	7.372	Dominates
4b	All patients undergo arthroplasty every 15 years regardless of treatment	12,841,524	8.831	1,454,115	–49,389,993	7.373	Dominates
4c	BPA dose for treating bleeding events assumed to be the same for all treatment groups	12,907,894	8.887	1,452,448	-49,256,203	7.387	Dominates
4d	Body weight 30% less than base case	17,736,773	8.867	2,000,271	–25,867,312	7.353	Dominates
4e	Starting age of 0	11,949,497	8.759	1,364,195	–43,179,956	8.431	Dominates
4f	No treatment-attributable reduction in mortality	9,423,757	5.611	1,679,480	–44,254,034	6.617	Dominates

BPA = bypassing agent; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-years; rFVIIa = recombinant factor VIIa; vs. = versus.

[a] CADTH correction of calculation errors in the model.

For the CADTH base case, a series of price reduction analyses were undertaken (Table 3). The results show that emicizumab will require a price reduction of approximately 42% to be cost-effective compared with on-demand BPA strategy at a willingness-to-pay threshold of $50,000 per QALY). When the price of emicizumab is reduced by approximately 45%, it becomes the dominant treatment strategy compared with on-demand BPA. Note that the threshold of $50,000 per QALY is conventionally accepted for decision-making across conditions in Canada. However, this threshold is not a rule but a guide; it is up to the decision-makers within each context and jurisdiction to define what constitutes good value for money.

Given that emicizumab is the dominant strategy compared with BPA prophylaxis, price-reduction analyses were not conducted against BPA prophylaxis.

Table 3: CADTH Reanalysis Price Reduction Scenarios

ICURs of Emicizumab Versus BPA On-Demand ($/QALY)		
Price	**Base-Case Analysis Submitted by Manufacturer**	**CADTH Base Case**
Submitted	**1,420,982**	**1,442,642**
10% reduction	1,094,102	1,108,291
15% reduction	928,477	934,593
20% reduction	762,851	776,631
25% reduction	597,225	607,226
30% reduction	431,600	439,248
40% reduction	100,348	106,130
45% reduction	Dominant	Dominant

BPA = bypassing agent; ICUR = incremental cost-utility ration.

Information on the Budget Impact Analysis

Manufacturer's Budget Impact Analysis

In Canada, patients with hemophilia A with inhibitors are typically treated initially with a gradually increasing dose of FVIII or ITI to render patients' immune systems tolerant to exogenous FVIII. Patients who respond to this approach are treated with FVIII, while patients who do not respond are treated with BPAs, either prophylactically or on-demand.

The manufacturer conducted a budget impact analysis (BIA) to assess the national budgetary implications of reimbursing emicizumab in Canada in the pediatric and adult population of patients with hemophilia A with inhibitors.[2] The BIA was conducted from the Canadian public health care payer perspective. A prevalence-based approach was taken using a three-year analysis time frame: reference year: 2018, year 1: 2019, year 2: 2020, year 3: 2021. A national perspective was used, where Quebec was excluded from the analysis. The aim of the BIA is to evaluate the impact of making emicizumab available for patients currently on prophylactic and/or on-demand BPAs. In the base case, the manufacturer assumed that patients currently on high-dose FVIII or ITI would not switch to emicizumab, which is consistent with the opinion of the clinical expert consulted by CADTH. Two BPA drugs (FEIBA and Niastase) are available to patients in Canada. The manufacturer assumed that patients receive one of these drugs but not a combination. Figure 2 presents a flow diagram of the treatments received by patients, with percentages based on the current market shares of drugs.

The submitted BIA was developed in Microsoft Excel and compared two budget scenarios: a reference scenario, in which patients were treated with BPAs (either prophylactically or on-demand) or factor VIII (high-dose or ITI); and a new treatment scenario, in which patients currently on BPAs (prophylactic or on-demand) may switch to prophylactic emicizumab. For both scenarios, the total cost was determined based on the number of patients likely to receive each type of treatment multiplied by the relevant per-patient health care cost associated with treatment (e.g., costs include drug acquisition cost [based on dosage and unit cost], hospitalization cost, and AE management costs). The budget impact was then calculated by subtracting the total cost of the reference scenario from the total cost of the new treatment scenario.

To determine the number of patients likely to receive BPAs or emicizumab, the manufacturer used the total number of patients with hemophilia A, as estimated using Statistics Canada estimates,[8,9] and assumed that 3% of these patients have FVIII inhibitors.[10] The resulting numbers of patients in Canada with hemophilia A with inhibitors were 79, 83, 89, and 96, respectively, in the base year 2018 and years 1 to 3 . These patients were then assumed to receive BPAs (FEIBA or Niastase) in proportion based on their market shares (Figure 2). Patients currently on FVIII treatment (i.e., high-dose FVIII or ITI) were assumed to continue on these drugs (in the base case). For the new treatment scenario, the analysis assumed that [redacted] of pediatric patients and [redacted] of adult patients who are currently on prophylactic BPA would switch to emicizumab in years 1, 2, and 3, respectively. Of the patients currently receiving on-demand BPAs, the uptake rate for emicizumab was assumed to be [redacted] in years 1, 2, and 3, respectively.

The key model parameters used in the manufacturer's submission can be found in Table 14. The manufacturer's estimate of the patient numbers in the reference scenario and new treatment scenario can be found in Table 20. Unit costs were based on the PMPRB

maximum average potential price, which represents a ceiling price for drug products at introduction in Canada.[17]

The manufacturer included an additional scenario extending the use of emicizumab to the non-inhibitor population. The non-inhibitor population was categorized based on severity of hemophilia. Patients with moderate or moderate hemophilia were assumed to receive one of two treatments: long-acting or short-acting FVIII (either prophylactically or on-demand) in proportion to their market shares, whereas patients with mild hemophilia received only short-acting FVIII (see Figure 3). The manufacturer's BIA compared two budget scenarios: a reference scenario, in which patients were treated with short-acting or long-acting FVIII (either prophylactically or on-demand), and a new treatment scenario, in which patients were assumed to switch to prophylactic emicizumab as follows: In years 1, 2, and 3, respectively, [redacted] of prophylactic severe hemophilia patients and [redacted] of on-demand severe hemophilia patients would adopt emicizumab. For the moderately severe population, a [redacted] adoption of emicizumab is assumed each year for both on-demand and prophylaxis. Patient with mild hemophilia were assumed not to switch to emicizumab. The key model parameters and assumptions used in the non-inhibitor population analysis can be found in Table 18 and Table 19. The manufacturer's estimate of the patient numbers in the reference scenario and new treatment scenario can be found in Table 21.

Manufacturer's Base Case

The manufacturer estimated that introducing emicizumab to the market will result in cost savings because emicizumab prophylaxis is less expensive than BPA prophylaxis. The manufacturer-estimated cost savings are $31,295,993 in year 1, $40,705,147 in year 2, and $48,991,658 in year 3, with three-year total savings of $120,992,798 (Table 4). The reason for the yearly increase in cost savings is that the manufacturer's analysis assumed that an increasing percentage ([redacted]) of prophylactic BPA patients will switch to emicizumab over three years. In the manufacturer's sensitivity analysis, results were most sensitive to BPA therapy costs (the total budget impact in year 1 ranged from cost savings of $17,359,050, when price of BPAs were reduced by 30%, to cost savings of $3,422,107, when price was reduced by 60% of base case values), and to changing inhibitor prevalence (year 1 cost savings of $47,044,395 when prevalence is estimated from the literature);22 see Table 30. A scenario analysis excluding non-drug medical costs (i.e., including drug acquisition costs only), per typical BIAs, resulted in cost savings of $30,928,588 in year 1, $40,229,306 in year 2, and $48,342,943 in year 3.

Table 4: Manufacturer's Base-Case Results (Inhibitor Population)

	Reference Scenario ($)			New Treatment Scenario ($)		
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
Pediatric[a]	1,809,545	1,962,047	2,594,269	734,865	868,952	1,086,943
Adult[a]	86,368,836	95,055,306	100,149,343	56,147,524	55,443,253	52,665,011
Total[a]	88,178,381	97,017,353	102,743,612	56,882,389	56,312,206	53,751,954
Incremental cost[b]	Ref	Ref	Ref	–31,295,993	–40,705,147	–48,991,658

Ref = reference.

[a] Factor VIII costs are excluded.

[b] Incremental costs are calculated as the difference between the total costs in the new treatment scenario and the reference scenario. Negative values denote cost savings.

In the non-inhibitor population analysis reported that, under the new treatment scenario, introducing emicizumab to the market will result in increased costs because emicizumab prophylaxis is more costly than long- and short-acting FVIII (prophylactically and on-demand). The manufacturer estimated that, based on the previously mentioned assumptions, the overall budget will increase by $60,549,175 in year 1, $68,316,619 in year 2, and $85,527,770 in year 3 for this population (Table 5). A scenario analysis excluding non-drug medical costs (i.e., including drug acquisition costs only), per typical BIAs, resulted in costs of $63,950,098 in year 1, $72,586,379 in year 2, and $90,826,076 in year 3 (Table 31).

Table 5: Manufacturer's Base-Case Results (Non-Inhibitor Populations)

	Reference Scenario ($)			New Treatment Scenario ($)		
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
Pediatric[a]	31,276,504	33,092,893	35,859,297	35,282,885	37,526,163	41,496,206
Adult[a]	330,298,360	347,389,479	370,949,693	403,932,273	434,833,041	478,585,930
Total[a]	378,665,983	404,042,586	434,554,366	439,215,158	472,359,205	520,082,136
Incremental cost[b]	Ref	Ref	Ref	60,549,175	68,316,619	85,527,770

Ref = reference.

[a] Factor VIII costs are excluded.

[b] Incremental costs are calculated as the difference between the total costs in the new treatment scenario and the reference scenario. Negative values denote cost savings.

Finally, aggregating the costs for patients with hemophilia A with and without inhibitors resulted in costs of $29,253,183 in year 1, $27,611,472 in year 2, and $36,536,112 in year 3 (Table 32).

Sources of Uncertainty Relating to the Manufacturer's Submission

CADTH identified the following limitations and sources of uncertainty relating to the manufacturer's BIA submission:

- **Estimate of relative treatment effect:** The manufacturer used an ABR of 18.6 for on-demand adult patients in its BIA; however, HAVEN 1 reported this value to be 23.3, which was also used in the CUA analysis.[11] This inconsistency in ABR has not been explained in the submission.
- **Hemophilia A population and inhibitor population estimates:** The manufacturer used data from a 2014 report produced by the Canadian Hemophilia Registry to estimate the total number of people with hemophilia A and the proportion of patients with FVIII inhibitors. More recent data from the Canadian Hemophilia Registry were used to estimate the number of patients with hemophilia A with FVIII inhibitors in Canada.[13]
- **Market uptake:** The clinical expert consulted by CADTH noted that the emicizumab uptake rate in the on-demand population is unlikely to be as low as that used in the manufacturer's BIA analysis (i.e., [redacted] in years 1, 2, and 3, respectively). Based on consultations with CBS and CADTH's clinical expert, CADTH assumed in the base case that emicizumab will be adopted by 100% of the pediatric and adult population in both BPA prophylactic and on-demand BPA patient groups.

- **Market shares of BPAs:** Market shares of BPAs used by the manufacturer were estimated from published literature[23,24] and feedback from clinicians and patient groups. CADTH obtained Canadian market share data of BPAs through CBS and used these data in CADTH reanalysis.
- **BPA unit costs:** The manufacturer used unit costs based on the PMPRB maximum average potential price, which represents a ceiling price for drug products at introduction in Canada. However, CBS provided current unit costs for FEIBA and Niastase, which were used in CADTH base case.
- **Average patient weight:** In the absence of Canadian data on body weight of patients with hemophilia A, the average patient weight in the BIA (for dose calculation) was based on an Australian non-interventional study undertaken by the manufacturer.[12] It is unclear how this body weight relates to the Canadian population.

CADTH Reanalyses

CADTH reanalysis accounted for the previously mentioned limitations in the manufacturer's budget impact model. A revised base-case analysis (CADTH base case) is based on the following modifications made to the manufacturer's model:

CADTH Base-Case Analysis for the Inhibitor Population

1. The ABR value for on-demand BPA patients was based on HAVEN 1 clinical trial literature[11] (23.3 bleeds instead of 18.6).
2. The number of patients with hemophilia A and the proportion with inhibitors was based on more recent 2017 estimates. Based on this, there were 372 pediatric and 2,426 adult patients with Hemophilia A in Canada and, out of these, 81 patients have FVIII inhibitors (27 pediatric and 54 adults).[13]
3. The expected uptake rate of emicizumab was revised as follows:
   - 100% of pediatric patients on prophylaxis will adopt emicizumab in years 1, 2, and 3
   - 100% of adult patients on prophylaxis will adopt emicizumab in years 1, 2, and 3
   - 100% of patients on on-demand treatment with BPAs will adopt emicizumab in years 1, 2, and 3.
4. The market shares of BPAs (FEIBA and Niastase) were revised as follows:
   - [redacted] of pediatric patients on BPAs were assumed to be treated with FEIBA (of these, [redacted] receiving FEIBA on-demand and [redacted] receiving it prophylactically), and [redacted] treated with Niastase (of these, [redacted] receiving Niastase on-demand and [redacted] receiving it as prophylaxis).
   - [redacted] of adult patients on BPAs were assumed to be treated with FEIBA (of these, [redacted] receiving FEIBA on-demand and [redacted] receiving it prophylactically), and [redacted] treated with Niastase (of these, [redacted] receiving Niastase on-demand and [redacted] receiving it as prophylaxis).
5. Unit costs were revised according to CBS data as follows:
   - FEIBA: [redacted]
   - Niastase [redacted]

6. CADTH base case (analyses 1 to 5).

Scenario analyses:

a. CADTH revised base case plus body weight of patients assumed to be ±30% that of base case.

b. CADTH revised base case plus body weight of patients assumed to be equal to average UK-based body weight, as reported by the manufacturer in the CUA.[2]

c. CADTH revised base case plus the number of treated bleeds per year for BPA prophylaxis and BPA on-demand treatments, based on the data provided by CBS from the Canadian Bleeding Disorders Registry, as follows: 4.8 and 8 treated bleeds per year in the pediatric and adult populations on BPA prophylaxis, respectively; and 15.02 and 23.18 treated bleeds per year in the pediatric and adult populations on BPA on-demand, respectively.

d. CADTH revised base case plus no wastage of emicizumab or BPA due to vial sharing.

e. CADTH revised base case plus including drug acquisition costs only (excluding hospitalization and AE management costs).

CADTH Base-Case Analysis for Non-Inhibitor Population

a. The number of patients with hemophilia A was estimated from the most recent 2017 Canadian Hemophilia Registry report data.[25] Based on this, 52%, 11%, and 37% of the pediatric population have severe, moderate, and mild hemophilia, respectively. Whereas 25%, 9%, and 66% of the adult population have severe, moderate, and mild hemophilia, respectively.

b. Revised CBS market share of FVIII products

- In the pediatric population, [redacted] of severe patients are assumed to be on long-acting and short-acting regimens, respectively, and [redacted] of moderate patients are assumed to be on long-acting and short-acting regimens, respectively.
- In the adult population, [redacted] of severe patients are assumed to be on long-acting and short-acting regimens, respectively, and [redacted] of moderate patients are assumed to be on long-acting and short-acting regimens, respectively.

c. According to revised CBS FVIII unit costs, the following products were used as proxies for short- and long-acting FVIII:

- short-acting FVIII: Xyntha [redacted]
- long-acting FVIII: Adynovate [redacted]

CADTH base-case reanalysis in the inhibitor population resulted in estimated cost savings of $32,920,731 in year 1, $34,750,021 in year 2, and $36,545,226 in year 3 (Table 6).

Table 6: CADTH Base-Case Results (Inhibitor Population)

	Reference Scenario ($)			New Treatment Scenario ($)		
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
Pediatric[a]	7,005,353	7,005,353	7,005,353	2,756,032	2,568,428	2,568,428
Adult[a]	54,073,613	54,073,613	56,707,499	25,402,203	23,760,517	24,599,198
Total[a]	61,078,966	61,078,966	63,712,852	28,158,235	26,328,945	27,167,626
Incremental cost[b]	Ref	Ref	Ref	–32,920,731	–34,750,021	–36,545,226

Ref = reference.

[a] Factor VIII costs are excluded.

[b] Incremental costs are calculated as the difference between the total costs in the new treatment scenario and the reference scenario. Negative values denote cost savings.

Detailed results of CADTH reanalysis and sensitivity analyses can be found in Table 33. Results of sensitivity analysis on the CADTH base case ranged from savings of approximately $23 million (when body weight was reduced by 30%) to $42.5 million (when body weight was increased by 30% of base case values) in year 1. When excluding non-drug–related costs (e.g., hospitalization and AE costs), CADTH base-case reanalysis estimated cost savings of $32,253,708 in year 1, $34,082,997 in year 2, and $35,853,064 in year 3 (Table 33).

CADTH base-case reanalysis of the non-inhibitor population estimated that the budget will increase by $76,431,845 in year 1, $90,122,437 in year 2, and $110,764,370 in year 3 in this population (Table 7). When excluding non-drug–related costs (hospitalization and AE costs), CADTH base-case reanalysis estimated costs of $78,793,929 in year 1, $93,062,975 in year 2, and $114,346,925 in year 3. The primary reason for the difference between the manufacturer's and CADTH's estimates in budget impact figures was the assumed proportion of patients who would receive emicizumab and the assumed unit cost of short- and long-acting FVIII (the manufacturer used Kogenate as a proxy for short-acting FVIII, priced at $1.2191/IU, and Eloctate was used as a proxy for long-acting FVIII, priced at $[redacted], while CADTH reanalysis used Xyntha as a proxy for short-acting FVIII, priced at $0.27, and Adynovate as proxy for long-acting FVIII, priced at $[redacted]). An additional analysis was performed using the average cost of Kogenate and Xyntha as a revised cost for short-acting FVIII and the average cost of Eloctate and Adynovate as a revised cost for long-acting FVIII in order to reflect the current market share of these products according to clinical expert advice. This scenario resulted in a budget increase of $27,386,495 in year 1, $35,639,441 in year 2, and $50,411,073 in year 3.

Table 7: CADTH Base Case Results (Non-Inhibitor Population)

	Reference Scenario ($)			New Treatment Scenario ($)		
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
Pediatric	10,795,947	11,080,655	11,466,731	17,203,776	18,609,009	20,647,766
Adult	83,647,335	86,052,555	89,453,712	153,671,350	168,646,638	191,037,047
Total	94,443,281	97,133,209	100,920,443	170,875,126	187,255,647	211,684,813
Incremental cost[a]	Ref	Ref	Ref	76,431,845	90,122,437	110,764,370

Ref = reference.

[a] Incremental costs are calculated as the difference between the total costs in the new treatment scenario and the reference scenario. Negative values denote cost savings.

CADTH Reanalyses Using the Inhibitor and Non-Inhibitor Populations

CADTH also evaluated the national budgetary implications of reimbursing emicizumab in Canada in the extended pediatric and adult population of patients with hemophilia A with and without inhibitors. CADTH estimated that the budget will increase by $43,511,114 in year 1, $55,372,417 in year 2, and $74,219,144 in year 3 in this population (Table 8). When excluding non-drug–related costs (hospitalization and AE costs), CADTH estimated costs of $46,540,221 in year 1, $58,979,978 in year 2, and $78,493,861 in year 3.

Table 8: CADTH Results in the Extended Population (Inhibitor and Non-Inhibitor)

	Reference Scenario ($)			New Treatment Scenario ($)		
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
Pediatric	20,509,923	20,794,631	21,180,708	22,668,432	23,886,061	25,924,817
Adult	149,722,835	152,128,055	159,549,814	191,075,441	204,409,042	229,024,847
Total	170,232,759	172,922,687	180,730,521	213,743,872	228,295,103	254,949,665
Incremental cost[a]	Ref	Ref	Ref	43,511,114	55,372,417	74,219,144

Ref = reference.

[a] Incremental costs are calculated as the difference between the total costs in the new treatment scenario and the reference scenario. Negative values denote cost savings.

If the cost savings in the inhibitor population is used to cross-subsidize the non-inhibitor population, CADTH estimates that this would cover 43% of the cost associated with reimbursing emicizumab in the non-inhibitor population in the first year. Stratification of cost in the non-inhibitor group (e.g., previously untreated population) was not feasible due to lack of data. It is important to note that the previously noted estimates only focus on the budget impact; however, given the absence of cost-effectiveness evidence for emicizumab in the non-inhibitor population, it is not possible to comment on the value of using emicizumab in the non-inhibitor population; i.e., what clinical benefit patients will receive from emicizumab against the cost incurred.

An exploratory price reduction analysis was conducted to explore potential scenarios in which the overall budget might be cost neutral if emicizumab is used in both inhibitor and non-inhibitor patients (under the coverage assumptions of CADTH base case). CADTH estimated that a price reduction of 39% would be required to achieve cost neutrality in year 1 (44% in year 2 and 49% in year 3). However, it is important to note that whether emicizumab represents a cost-effective treatment in patients without inhibitors remains unknown, which is a limitation of this analysis.

An additional scenario analysis was performed by assuming that 100% of both inhibitor and non-inhibitor populations with severe and moderate hemophilia would use emicizumab. This scenario resulted in a total budget impact (for both inhibitor and non-inhibitor populations) of $434,154,046 in year 1, $408,625,306 in year 2, and $424,260,072 in year 3 (Table 34). For this scenario, an 80% price reduction would be required to achieve cost neutrality to cover emicizumab in years 1 to 3. If non-drug–related costs (i.e., hospitalization and AE costs) are excluded from the analysis, CADTH estimated a budget impact of $434,821,070 in year 1, $409,292,330 in year 2, and $424,952,234 in year 3 (Table 34). Given that prophylaxis and on-demand treatments are associated with higher non-drug health care costs compared with

emicizumab, including these costs in the analysis reduced the difference in total costs between the reference scenario and the new drug scenario in the BIA.

The manufacturer considered the analysis from a national perspective. CADTH has provided the results by province based on the assumption of equal prevalence across jurisdictions in Appendix 4.

Issues for Consideration

- The HAVEN 1 clinical trial population is not fully representative of the Canadian population. The Canadian Hemophilia Registry reports that 26% of hemophilia patients with FVIII inhibitors have a mild-to-moderate form of the disease,[10] whereas only 6% of the patients in the clinical trial HAVEN 1 had mild-to-moderate forms of the disease. Therefore, the model may be overestimating bleeding rates in the Canadian population.
- Emicizumab is likely to be used in patients without inhibitors. CADTH is unable to comment on the cost-effectiveness of emicizumab in the non-inhibitor population given that the manufacturer did not provide any evidence of effectiveness in this population. However, the manufacturer has assessed the budget impact of introducing emicizumab in the non-inhibitor population in the BIA submission based on HAVEN 3 and 4 estimates.

Conclusions

The manufacturer evaluated the cost-effectiveness and budget impact of emicizumab prophylaxis in patients with hemophilia A with inhibitors. Manufacturer's cost-effectiveness analysis estimated that emicizumab was a dominant strategy (i.e., lower costs and higher QALYs) compared with BPA prophylaxis in both adult and pediatric populations; however, compared with on-demand BPAs, the ICUR for emicizumab was $1,420,982 per QALY for adult patients and $1,348,371 per QALY for pediatric patients. CADTH identified the key limitation with the manufacturer's approach as the two-state model used, which did not allow explicit modelling of key aspects of hemophilia or treatments. This made the assessment of model validity challenging; thus, the cost-effectiveness results should be interpreted with caution. CADTH reanalyses addressed some of the identified limitations but could not account for the model structure. Based on CADTH estimates, emicizumab remained a dominant strategy compared with BPA prophylaxis, but was associated with an ICUR of $1,442,642 per QALY when compared with on-demand BPAs. Emicizumab would require a price reduction of 42% to be cost-effective at a conventionally accepted willingness to pay of $50,000 per QALY. The manufacturer did not evaluate the cost-effectiveness of emicizumab in the non-inhibitor population; CADTH reanalyses also did not include this population due to lack of evidence.

The manufacturer also conducted a BIA of reimbursing emicizumab in Canada (except Quebec). CADTH reanalysis of the BIA used up-to-date (2017) figures for population prevalence[13,25] and market shares, and estimated cost savings of $32,920,731 (in year 1, and slightly higher in subsequent years) after making emicizumab available in the inhibitor population. For the non-inhibitor population, the CADTH reanalysis estimated excess costs of $76,431,845 in year 1, $90,122,437 in year 2, and $110,764,370 in year 3. For the combined population of inhibitors and non-inhibitors, CADTH reanalysis estimated excess cost. When excluding non-drug–related costs, CADTH estimated that introducing emicizumab for both the inhibitor and non-inhibitor populations will result in excess costs of $46,540,221 in year 1, $58,979,978 in year 2, and $78,493,861 in year 3.

In summary, in the inhibitor population, emicizumab is the dominant treatment compared with BPA prophylaxis but, compared with on-demand BPA, emicizumab will require a price reduction of 42% to be cost-effective (at a willingness to pay of $50,000 per QALY). The cost-effectiveness of emicizumab in the non-inhibitor population remains unknown. CADTH estimated that reimbursing emicizumab in patients with hemophilia A with inhibitors will result in cost savings, but reimbursing it in both inhibitor and non-inhibitor populations would result in an increased cost of $78,493,861 (in year 3) when considering only drug costs. CADTH noted that there is paucity of evidence, both on efficacy and utilization of drugs considered in this report; therefore, the results should be interpreted with consideration of the assumptions outlined in the previously described analyses.

Appendix 1: Cost Comparison

The comparators presented in the following table have been deemed to be appropriate by clinical experts. Costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

Table 9: CADTH Cost Comparison Table for Treatments in Hemophilia A With Inhibitors [a]

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Emicizumab as prophylaxis	**30 mg/mL**	**Vial of solution for SC injection**	[redacted][b]	**3 mg/kg once weekly for 4 weeks, followed by 1.5 mg/kg once weekly as long-term prophylaxis[c]**	**Year 1:** [redacted][d] **Year 2+:** [redacted][d]	**Year 1:** [redacted][d] **Year 2+:** [redacted][d]
	60 mg/0.4 mL		[redacted][b]		**Year 1:** [redacted][d] **Year 2+:** [redacted][d]	**Year 1:** [redacted][d] **Year 2+:** [redacted][d]
	105 mg/0.7 mL		[redacted][b]		**Year 1:** [redacted][d] **Year 2+:** [redacted][d]	**Year 1:** [redacted][d] **Year 2+:** [redacted][d]
	150 mg/mL		[redacted][b]		**Year 1:** [redacted][d] **Year 2+:** [redacted][d]	**Year 1:** [redacted][d] **Year 2+:** [redacted][d]
Prophylaxis Bypassing Agent						
aPCC (FEIBA)	400 to 1,200 units/20 mL 1,750 to 3,250 units/50 mL[e]	Vial of powder for IV injection or infusion	1.75[f]	298 IU/kg once weekly[h]	5,215.00[i]	1,903,475.00
rFVIIa (Niastase)	1 mg (50 KIU/vial) 2 mg (100 KIU/vial) 5 mg (250 KIU/vial) 8 mg (400 KIU/vial)[e]	Vial of powder for IV injection	1.17[g]	630 mcg/kg once weekly[h]	7,398.78[i]	2,700,555.80

aPCC = activated prothrombin complex concentrate; FEIBA = factor eight inhibitor bypassing activity; rFVLLa = recombinant factor VIIa; SC = subcutaneous.

[a] Based on a patient weight of 70 kg.

[b] Manufacturer-submitted price per vial.[2]

[c] From product monograph.

[d] Assumes wastage of partially used vials. For example, a 70 kg patient would require a dose of 210 mg equivalent to seven 30mg/mL vials per week for the first four weeks, and a dose of 105 mg equivalent to four 30 mg/mL vials per week as long-term prophylaxis. This will result in an annual cost of $[redacted] for the first year and of $[redacted] for subsequent years.

[e] From product monograph.

[f] Unit cost based on the patented medicine prices review board (PMPRB) maximum average potential price (MAPP).[17]

[g] Unit cost for 1mg/vial based on the PMPRB MAPP.[17]

[h] Dosage provided in product monograph.[1]

[i] Assumes no wastage given that any unused product will be used in the next patient.

Appendix 2: Additional Information

Table 10: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments Reviewer to provide comments if checking “no”	None		
Was the material included (content) sufficient?		X	
Comments Reviewer to provide comments if checking “poor”	None		
Was the submission well organized and was information easy to locate?	X		
Comments Reviewer to provide comments if checking “poor”	None		

Table 11: Authors Information

Authors of the Pharmacoeconomic Evaluation Submitted to CADTH

☐ Adaptation of global model/Canadian model done by the manufacturer

☒ Adaptation of global model/Canadian model done by a private consultant contracted by the manufacturer

☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the manufacturer

☐ Other (please specify)

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis	X		

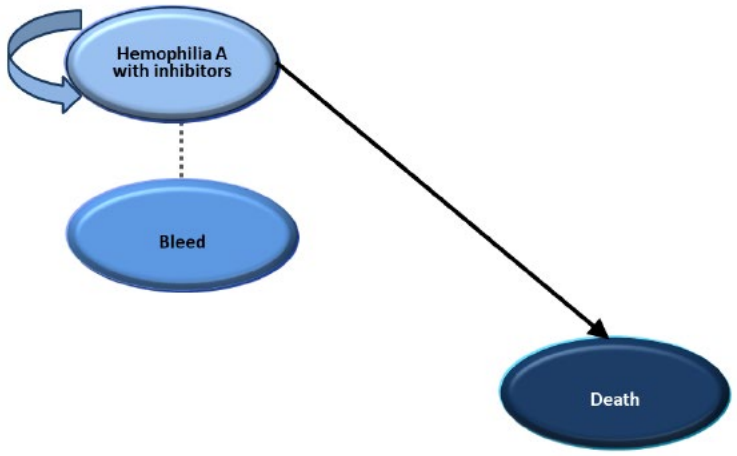
Appendix 3: Detailed Information — Economic Submission

Manufacturer's Model Structure

The manufacturer submitted a cost-utility analysis comparing the following treatments for hemophilia A with factor VIII inhibitors: prophylaxis with emicizumab, prophylaxis with bypassing agents (BPA), and on-demand (episodic) BPA.[2] Details of the Markov structure are shown in Figure 1. The manufacturer developed a Markov model based on the following two health states: alive with hemophilia A with inhibitors (and receiving one of the three treatments previously mentioned); and dead. The model uses a one-year cycle length. All patients in the model started in the alive state and could experience bleeding events or death during a model cycle (the risk of these events depended on the treatment being received).

The model population, treatment response, and adverse event rates were based on two studies: HAVEN 1 — a phase III randomized controlled trial in adults and adolescents (≥ 12 years old) comparing the efficacy, quality of life, and safety of emicizumab prophylaxis with on-demand treatment with BPAs; and a single-arm, non-interventional study evaluating bleeding incidence, quality of life, and safety in patients with hemophilia A with inhibitors receiving BPA prophylaxis.

Figure 1: Markov Model Structure



Source: Manufacturer's submission.[2]

Table 12: Summary of the Manufacturer's Economic Submission

Drug Product	Emicizumab (Hemlibra)
Study Question	Is emicizumab a cost-effective alternative to prophylactic and on-demand treatment with bypassing agents (BPAs) for hemophilia A patients with inhibitors in Canada?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adult and pediatric patients with hemophilia A with inhibitors
Treatment	Emicizumab (3 mg/kg once weekly for 4 weeks, followed by 1.5 mg/kg once weekly)
Outcome	Life years (LY) Quality-adjusted life-years (QALY)
Comparators	Prophylaxis with BPAs • Factor VIII inhibitor bypassing activity (FEIBA) (298 IU/kg weekly) • Recombinant activated human FVIIa (Niastase) (630 mcg/kg weekly) On-demand treatment with BPAs • Factor VIII inhibitor bypassing activity (FEIBA) (132 IU/kg per bleed) • Recombinant activated human FVIIa (Niastase) (296 mcg/kg per bleed)
Perspective	Canadian health care system
Time Horizon	Lifetime (up to the age of 100)
Results for Base Case	• Emicizumab vs. prophylactic BPAs: emicizumab dominant treatment; i.e., it had lower costs and higher QALYs • Emicizumab vs. on-demand BPAs: emicizumab was associated with an incremental cost per QALY of $1,420,982
Key Limitations	CADTH identified the following limitations: • The economic analysis was based on an unconventional two-state model that assumed constant treatment-specific utility values (resulting in significant uncertainty in model results). Furthermore, a key clinical aspect (arthropathy) was not explicitly included in the model. • The manufacturer used an unpublished, observational, single-arm, non-interventional study to estimate bleeding rate and quality of life in patients receiving BPA prophylaxis. This non-randomized evidence was used alongside and directly compared with randomized trial data for emicizumab prophylaxis and on-demand BPA. Because key model parameters for the three treatment groups were based on two different data sources and study designs, there were inconsistencies in the relationship between bleeding rates and utility values in the three treatment groups. • The manufacturer assumed that patients receiving on-demand BPA would require an arthroplasty every 15 years but patients on prophylactic emicizumab or BPAs were assumed to not require any arthroplasty; however, no evidence was provided to support this assumption. Moreover, the manufacturer assumed a utility value of zero for one month for patients undergoing arthroplasty — this assumption is also not supported by evidence or by the clinical expert consulted by CADTH. • Follow-up in the HAVEN 1 study is short (24 weeks), which is not long enough to make lifetime assumptions regarding treatment effectiveness or to demonstrate the safety of emicizumab.

CADTH Estimate(s)	CADTH reanalyses could not address the most important limitation (inappropriate modelling approach), which introduced significant uncertainty in the analysis. However, CADTH reanalyses addressed the limitations related to estimates of relative treatment effect and arthroplasties. Instead of using the lower-quality NIS, the annual bleeding rate for BPA prophylaxis was estimated by applying the relative bleeding risk compared with on-demand BPA, as reported in a published study identified by the manufacturer in a systematic review. Further, patients on on-demand BPA treatment were assumed to experience a maximum of two arthroplasties based on consultation with CADTH's clinical expert. Finally, quality-of-life impact of arthroplasty was modelled by applying arthroplasty-related disutility of –0.39 for one month. Based on CADTH estimates: • Emicizumab dominated BPA prophylaxis; i.e., it had lower incremental costs and higher incremental QALYs. • The resulting ICUR for emicizumab versus on-demand BPAs was $1,442,642 per QALY gained.

BPA = bypassing agent; FEIBA = factor eight inhibitor bypassing activity; FVIIa = factor VIIa; ICUR = incremental cost-utility ratio; LY = life-year; NIS = non-interventional study; QALY = quality-adjusted life-year; vs. = versus.

Table 13: Data Sources

Data Input	Description of Data Source	Comment
Baseline characteristics	Based on patient characteristics in the clinical trial HAVEN 1[11]	The clinical trial includes more severe patients than the average patient population in Canada; therefore, the model may be overestimating the bleeding rates from the Canadian perspective.
Efficacy	Efficacy on reduction of bleeding rate was obtained from the HAVEN 1 clinical trial and the NIS	Follow-up is not sufficiently long to make lifetime conclusions regarding the efficacy of emicizumab. Because key model parameters for the three treatment groups were based on two different data sources and study designs (NIS and an RCT, HAVEN 1), CADTH noted inconsistency in the relationship between bleeding rates and utility values in the three treatment groups; i.e., patients on BPA prophylaxis (in the NIS) had, on average, lower bleeding rates but also had lower average utility values compared with on-demand BPA patients in the HAVEN 1 trial.
Natural history	HAVEN clinical trial[11]	Adequate; however, given the lack of long-term data, natural history is based on short-term follow-up.
Utilities	The utility values for emicizumab and on-demand treatment were obtained from the HAVEN 1 clinical trial. Utilities for prophylaxis with BPAs were sourced from the NIS.	Inappropriate. The manufacturer used treatment-specific utilities as a result of the model structure limitations; however, utilities should reflect health states in the model, per CADTH guidelines.[3] As previously noted, due to the use of two different data sources and study designs (NIS and RCT), CADTH noted inconsistency in the relationship between bleeding rates and utility values in the three treatment groups; i.e., patients on BPA prophylaxis (in the NIS) had, on average, lower bleeding rates but also had lower average utility values compared with on-demand BPA patients in the HAVEN 1 trial.
Adverse events	Annual adverse event rates were derived from the clinical trial HAVEN 1 and the NIS (appendicitis perforated, compartment syndrome, device related infection, device related sepsis,	Partially appropriate. Additionally, concomitant use of emicizumab prophylaxis with an activated prothrombin complex concentrate (FEIBA) to treat episodic bleeds is associated with thrombotic microangiopathy and thromboembolism risk when a cumulative amount of > 100 U/kg per 24 hours aPCC was administered for 24 hours or

Data Input	Description of Data Source	Comment
	gastrointestinal hemorrhage, hemorrhage, iron deficiency anemia, muscle hemorrhage, pneumonia, skin necrosis, subdural hemorrhage, thrombotic microangiopathy, and urinary tract infection).	more. This increased risk was not accounted for in the model.
Mortality	Additional mortality risk for hemophilia patients above the general population was incorporated from the literature[16] and was stratified according to disease severity. The SMR was assumed to be constant over the model's lifetime horizon and was applied to background Canadian-specific all-cause mortality rates.	Partially appropriate. The clinical expert consulted by CADTH considered this assumption to be plausible; however, no evidence was provided by the manufacturer to support this assumption.
Resource Use and Costs		
Drug	Drug costs were based on the manufacturer's submitted price and the New Patented Medicines Reported to PMPRB.	Appropriate source given that there are no other publicly available prices for Canada.
Administration	The model does not include physician, monitoring for neutralizing antibodies, and drug administration costs such as CVAD placement.	Appropriate.
AEs	Hospitalization and inpatient costs were obtained from the Ontario Case Costing Initiative.[18] Surgery costs (arthroplasty) were obtained from the Canadian Institute for Health Information.[19]	Appropriate.

AEs = adverse events; aPCC = activated prothrombin complex concentrate; BPA = bypassing agent; CVAD = central venous access devices; FEIBA = factor eight inhibitor bypassing activity; NIS = non-interventional study; PMPRB = Patented Medicine Prices Review Board; RCT = randomized controlled trial; SMR = standardized mortality rate.

Table 14: Manufacturer's Key Assumptions

Assumption	Comment
UK-specific body weight by age was assumed to be reflective of the Canadian population	Canadian body weight was not used. It is unclear how UK body weight compares with body weight of the Canadian patients.
There is zero treatment discontinuation	Inappropriate. Previous evidence has shown that adherence to BPA prophylaxis in patients without inhibitors is likely to be between 26% and 96%.[21] Higher assumed adherence may overestimate the effectiveness of prophylaxis.
Patients experience a constant, treatment-specific quality of life (utility) throughout their lifetime	Inappropriate. The use of treatment-specific utilities is discouraged as the more transparent approach is to assign utility values to clinically relevant health states, per CADTH guidelines.[3]

Assumption	Comment
	Estimated QALYs may be incorrect because utility values are based on a single fitted utility at the end of the follow-up period for each treatment group — this does not take account variation in quality of life during the follow-up.
Costs of CVAD placement are not included	Inappropriate, but these costs will be relatively minor compared with drug acquisition costs.
Prophylactic patients are assumed not to require arthroplasties due to a reduction in number of bleeds	Acceptable.
Patients receiving on-demand BPA are assumed to require an arthroplasty every 15 years (at ages 25, 40, 55, and 70, resulting in four arthroplasties throughout their lifetime)	Inappropriate. The clinical expert suggested that an average patient is expected to undergo two arthroplasties during lifetime.
The utility of arthroplasty is assumed to be 0 for a one-month duration	Inappropriate. This assumption is not supported by evidence or by the clinical expert consulted by CADTH.
Patients under episodic BPAs experience a standardized mortality ratio (SMR) of severe patients throughout their lifetime, whereas patients under emicizumab and BPA prophylaxis will have an SMR of mild-to-moderate patients	Acceptable; however, there is no direct evidence to support the mortality benefit of prophylaxis with emicizumab or BPA compared with on-demand treatment.
For patients on emicizumab, 70% of the bleeds are treated with rFVIIa and 30% are treated with aPCC	Acceptable. However, concomitant use of emicizumab prophylaxis with an activated prothrombin complex concentrate such as FEIBA to treat episodic bleeds is associated with thrombotic microangiopathy and thromboembolism risk when a cumulative amount of > 100 U/kg per 24 hours aPCC was administered for 24 hours or more. Physicians are therefore likely to preferentially choose Niastase over FEIBA to treat bleeds for patients on emicizumab prophylaxis.
The model assumes (based on the HAVEN 1 trial data) that the quantity of BPA used to treat bleeding events is different for different treatment groups	Acceptable. Clinical evidence for this assumption is not clear in the submission; however, it was considered acceptable by the clinical expert consulted by CADTH.

aPCC = activated prothrombin complex concentrate; BPA = bypassing agent; CVAD = central venous access devices; FEIBA = factor eight inhibitor bypassing activity; QALY = quality-adjusted life-year; rFVIIa = recombinant factor VIIa; SMR = standardized mortality rate.

Manufacturer's Results

Table 15: Manufacturer's Scenario Analyses

	Emicizumab Versus BPA Prophylaxis			Emicizumab Versus On-Demand		
Scenario	ΔQALY	ΔCost ($)	Cost per QALY gained ($)	ΔQALY	ΔCost ($)	Cost per QALY gained ($)
Base case	7.397	–55,652,622	Dominates	8.980	12,760,415	1,420,982
Time horizon: 60 years	7.072	–53,176,061	Dominates	7.877	11,648,039	1,478,744
Time horizon: 40 years	5.630	–42,447,895	Dominates	5.437	8,522,636	1,567,482
Discount rate: 0%	11.198	–84,336,860	Dominates	15.339	20,864,087	1,360,214
Discount rate: 3%	5.269	–39,646,605	Dominates	5.838	8,590,500	1,471,432
Body weight: UK-based –20% by age	7.413	–54,531,769	Dominates	122.422[a]	–2,209,845[a]	–18,051[a]
Body weight: UK-based +20% by age	7.368	–54,543,369	Dominates	179.176[a]	–10,303,314[a]	–57,504[a]
Starting age: 28 (HAVEN 1 median age)	6.744	–50,850,718	Dominates	8.557	12,085,498	1,412,287
Starting age: 8.5 (HAVEN 2 median age)	8.206	–54,723,357	Dominates	9.070	12,924,705	1,424,922
Starting age: 0	8.420	–48,812,843	Dominates	8.882	11,976,886	1,348,371
Hospitalization cost: –50%	7.371	–55,400,734	Dominates	8.966	13,024,897	1,452,655
Hospitalization cost: +50%	7.387	–55,920,057	Dominates	8.968	12,602,630	1,405,323
Hospitalization cost: Literature[26]	7.361	–55,445,067	Dominates	8.968	12,909,142	1,439,451
Arthroplasty for on-demand patients: 2 surgeries	7.410	–55,680,696	Dominates	8.937	12,828,40	1,435,369
SMR: 1.00	7.528	–56,774,746	Dominates	9.610	13,448,157	1,399,392
SMR: 1.40	7.239	–54,577,172	Dominates	8.364	12,165,347	1,454,489
Arthroplasty cost: –50%	7.371	–55,651,889	Dominates	8.982	12,789,704	1,423,929
Arthroplasty cost: +50%	7.384	–55,652,576	Dominates	9.002	12,768,631	1,418,497
Market shares — prophylactic: 100% aPCC	7.393	–61,539,528	Dominates	8.975	12,793,040	1,425,391
Market shares — on-demand: 100% rFVIIa	7.393	–56,902,256	Dominates	8.975	10,976,940	1,223,020
Dosing: values from product monograph	7.365	–55,669,103	Dominates	8.955	12,857,495	1,435,712
AE costs: literature –20%	7.375	–55,637,816	Dominates	8.976	12,771,365	1,422,854
AE costs: literature +20%	7.407	–55,688,466	Dominates	9.022	12,803,236	1,419,102
Perspective: societal (human capital)	7.372	–55,702,370	Dominates	8.973	12,739,311	1,419,752

	Emicizumab Versus BPA Prophylaxis			Emicizumab Versus On-Demand		
Perspective: societal (friction method)	7.384	–55,656,343	Dominates	8.942	12,768,756	1,427,875
Utility values: HAVEN 1 -20%	5.908	–55,665,040	Dominates	7.203	12,787,428	1,775,362
Utility values: HAVEN 1 +20%	8.820	–55,656,622	Dominates	10.739	12,783,343	1,190,373
Disutility for arthroplasty: 0	7.382	–55,659,363	Dominates	8.848	12,797,064	1,446,215
Days hospitalized: 0	7.379	–55,128,679	Dominates	8.984	13,199,875	1,469,196
Days hospitalized: +50%	7.376	–55,212,843	Dominates	8.960	13,192,238	1,472,327
Annual bleed rate: -20% for all comparators	7.416	–53,439,459	Dominates	8.985	16,120,170	1,794,198
Annual bleed rate: +20% for all comparators	7.374	–57,879,385	Dominates	8.969	9,489,256	1,058,008
Clinical inputs: Indirect treatment comparison	7.333	–49,438,695	Dominates	8.966	12,827,121	1,430,566

Δ = utility unit; AE = adverse event; aPCC = activated prothrombin complex concentrate; BPA = bypassing agent; QALY = quality-adjusted life-years; SMR = standardized mortality ratio.

[a] Value could not be replicated.

Appendix 4: Detailed Information — Budget Impact Submission

Methods

The submitted budget impact analysis was developed in Microsoft Excel and compared two budget scenarios: a reference scenario, where patients were treated with bypassing agents (BPAs) (either prophylactically or on-demand) or factor (F)VIII (high-dose or immune tolerance induction), and a new treatment scenario, where patients currently on BPAs (prophylactic or on-demand) may switch to prophylactic emicizumab. The total cost for each scenario was calculated based on the estimated number of patients likely to receive each treatment multiplied by the per-patient costs associated with the treatment, including both the drug acquisition cost (based on dosage and unit cost) and treatment-related health system costs (i.e., hospitalization cost and adverse event management cost). The budget impact was then calculated by subtracting the total cost of the reference scenario from the total cost of the new treatment scenario.

Table 16 summarizes the key model parameters used in the manufacturer's submission, and Figure 2 shows the market shares for the inhibitor population.

Table 16: Manufacturer's Regimen and Cost Inputs (Inhibitor Population)

Parameter	Estimate		Source
	Pediatric	Adult	
Patient weight	[redacted]	[redacted]	Roche Australia study[12]
Treated Bleeds per Year			
Hemlibra	0.2	2.9	Oldenburg et al., Young et al.[27,28]
BPA (Prophylaxis)	17.2	14.9	Oldenburg et al., Young et al.[27,28]
BPA/FVIII (On-demand)	21.5	18.6	Oldenburg et al., Young et al.[27,28]
Dosage			
Hemlibra (Loading dose)	3.0 mg/kg q.w., weeks 1 to 4		Oldenburg et al., Young et al., product monograph[1,27,28]
Hemlibra (Maintenance dose)	1.5 mg/kg q.w., weeks 5+		Oldenburg et al., Young et al., product monograph[1,27,28]
FEIBA (Prophylaxis)	4 x 75 IU/kg/week		FEIBA monograph[29]
FEIBA (On-demand)	2 x 75 IU/kg/bleed		FEIBA monograph[29]
Niastase (Prophylaxis)	90 mcg/kg/day		Konkle et al.[14]
Niastase (On-demand)	3 x 90 mcg/kg/bleed		Niastase monograph[30]
FVIII (On-demand)	2 x 50 IU/kg/bleed		AHCDC guideline[31]
Wastage			
Hemlibra	[redacted]	[redacted]	Roche data on file
FEIBA	[redacted]	[redacted]	Roche data on file
Niastase	[redacted]	[redacted]	Roche data on file
FVIII	[redacted]	[redacted]	Roche data on file
Prices			
Hemlibra	[redacted]		Manufacturer's submission[2]
FEIBA	$1.7500/IU		PMPRB[17]

Parameter	Estimate		Source
	Pediatric	Adult	
Niastase	$1.1744/mcg		PMPRB[17]
FVIII	$1.2191/IU		PMPRB[17] Kogenate 500 was used as proxy

AHCDC = Association of Hemophilia Clinic Directors of Canada; BPA = bypassing agent; FEIBA = factor eight inhibitor bypassing activity; FVIII = factor VIII; IU = international units; PMPRB = Patented Medicine Prices Review Board; q.w. = once weekly.

Figure 2: Inhibitor Population Flow Diagram

REDACTED

Source: Manufacturer's submission.[2]

[a] No adoption was assumed from the high-dose factor VIII or immune tolerance induction populations; however, a scenario analysis presented by the manufacturer explored this assumption.

The manufacturer assumed that [redacted] (e.g., out of the [redacted] pediatric patients treated with BPAs), [redacted] of the [redacted] patients treated with factor eight inhibitor bypassing activity (FEIBA) and [redacted] of the [redacted] patients treated with Niastase were treated prophylactically [redacted] of the pediatric population treated with BPAs (either FEIBA or Niastase) were treated prophylactically, whereas 54% were treated on-demand. Manufacturer's submission also assumed that [redacted] of the adult population treated with BPAs (either FEIBA or Niastase) were treated prophylactically, whereas [redacted] were treated on-demand.

The manufacturer's base-case analysis estimates the number of patients with hemophilia A with inhibitors eligible for emicizumab prophylaxis over a three-year time horizon. The manufacturer considered the full indicated population (children and adults with hemophilia A with inhibitors) and conducted a scenario analysis to assess the impact of the potential use in a non-inhibitor population. Assumptions made by the manufacturer for use in the model can be found in Table 17.

Table 17: Assumptions Used in Manufacturer's Budget Impact Analysis for the Inhibitor Population and Revised in CADTH's Reanalyses

Manufacturer Base-Case Assumption (as Provided in its Budget Impact Analysis)	Revised Assumption for CADTH Reanalysis Restricted to the Indicated Population	Additional CADTH Analyses, Reported in Sections 3.5.2 and 3.5.3
Data from a 2014 report produced by the Canadian Hemophilia Registry was extrapolated using Statistics Canada values in order to estimate the total number of people with hemophilia A. The same 2014 report was used to estimate the proportion of the hemophilia A population with FVIII inhibitors; this proportion was assumed to remain constant every year.	The number of patients with hemophilia A and the proportion with inhibitors was based on the most recent 2017 estimates from the Canadian Hemophilia Registry.[13] Based on this, there were 372 pediatric and 2,426 adult patients with Hemophilia A in Canada, and out of these, 81 patients have FVIII inhibitors (27 pediatric and 54 adults).	None.
25% of the inhibitor population was considered pediatrics (< 12 years old) in the base year (2018).	According to 2017 data,[13] 33% of the population was considered pediatric in 2017. This value was used for 2018.	None.
In the absence of Canadian data on the body weight of patients with hemophilia A, average patient weight in the BIA (for dose calculation) was based on an Australian non-interventional study undertaken by the manufacturer.[12]	None.	It is unclear how Australian body weight compares with body weight of the Canadian patients. To address uncertainty around body weight assumptions, and potential differences between Australian and Canadian weights, CADTH reanalysis conducted sensitivity analyses to assess the impact of using lower body weight. An additional scenario used average UK-based weights reported by the manufacturer in the PE submission.[2]
Annual treated bleeds derived from HAVEN 1 and HAVEN 2 studies. Treated bleeds per year estimates for the adult population used by the manufacturer are 2.9, 14.9, and 18.6 for patients on emicizumab, BPA prophylaxis, and BPA on-demand, respectively.	The manufacturer used an ABR of 18.6 for on-demand adult patients in its BIA; however, HAVEN 1 reported this value to be 23.3, which was also used in the CUA analysis.[11] This inconsistency in ABR has not been explained in the submission. The HAVEN 1 value was used in CADTH reanalysis.	In a scenario analysis, CADTH used the number of treated bleeds per year for BPA prophylaxis and BPA on-demand treatments based on the data provided by CBS from the CBDR, which are as follows: 4.8 and 8 treated bleeds per year in the pediatric and adult population on BPA prophylaxis, respectively; and 15.02 and 23.18 treated bleeds per year in the pediatric and adult population on BPA on-demand, respectively.
Wastage of dosage regimens for pediatric patients are assumed to be [redacted] for emicizumab, FEIBA, Niastase, and FVIII respectively. Wastage of dosage regimens for adult patients are [redacted] for emicizumab, FEIBA, Niastase, and FVIII, respectively.	No change.	In a scenario analysis, CADTH explored the assumption of no wastage of BPA or emicizumab due to vial sharing.
Dosage based on product monograph and clinical trial data.	No change.	None.
Non-drug medical costs (hospitalization and adverse event management) included.	No change.	In a scenario analysis, CADTH excluded non-drug medical costs.

Manufacturer Base-Case Assumption (as Provided in its Budget Impact Analysis)	Revised Assumption for CADTH Reanalysis Restricted to the Indicated Population	Additional CADTH Analyses, Reported in Sections 3.5.2 and 3.5.3
Market shares of comparator products: • [redacted] of pediatric patients on BPAs are assumed to be treated with FEIBA (of these, [redacted] receiving FEIBA on-demand and [redacted] receiving it prophylactically), and [redacted] treated with Niastase (of these, [redacted] receiving Niastase on-demand and [redacted] receiving it as prophylaxis) • [redacted] of adult patients on BPAs are assumed to be treated with FEIBA (of these, [redacted] receiving FEIBA on-demand and [redacted] receiving it prophylactically), and [redacted] treated with Niastase (of these [redacted] receiving Niastase on-demand and [redacted] on receiving it as prophylaxis) • [redacted] of the pediatric population treated with BPAs was treated prophylactically and on-demand, respectively. [redacted] of the adult population treated with BPAs was treated prophylactically and on-demand, respectively.	CADTH used the following data provided by CBS: • [redacted] of pediatric patients on BPAs are assumed to be treated with FEIBA (of these, [redacted] receiving FEIBA on-demand and [redacted] receiving it prophylactically), and [redacted] treated with Niastase (of these, [redacted] receiving Niastase on-demand and [redacted] receiving it as prophylaxis) • [redacted] of adult patients on BPAs are assumed to be treated with FEIBA (of these, [redacted] receiving FEIBA on-demand and [redacted] receiving it prophylactically), and [redacted] treated with Niastase (of these [redacted] receiving Niastase on-demand and [redacted] on receiving it as prophylaxis) • [redacted] of the pediatric population treated with BPAs was treated prophylactically and on-demand, respectively. [redacted] of the adult population treated with BPAs was treated prophylactically and on-demand, respectively.	None.
Proportion of market adopting emicizumab: • [redacted] of pediatric patients on prophylaxis will adopt emicizumab in years 1, 2, and 3 • [redacted] of adult patients on prophylaxis will adopt emicizumab in years 1,2 and 3 • [redacted] of patients on on-demand treatment with BPAs will adopt emicizumab in years 1, 2, and 3.	Based on the advice from CBS and the clinical expert consulted by CADTH, the following market uptake estimates were used: • 100% of pediatric patients on prophylaxis will adopt emicizumab in years 1, 2, and 3 • 100% of adult patients on prophylaxis will adopt emicizumab in years 1, 2, and 3 • 100% of patients on on-demand treatment with BPAs will adopt emicizumab in years 1, 2, and 3.	None.
No adoption of emicizumab in ITI population.	No change.	None.
FEIBA priced at $1.75/IU and Niastase at $1.17444/mcg.	CADTH reanalyses was based on revised costs of FEIBA priced at [redacted], and Niastase at	None.

ABR = annual bleeding rate; BIA = budget impact analysis; CBDR = Canadian Bleeding Disorders Registry; CBS = Canadian Blood Services; CUA = cost-utility analysis; FEIBA = factor eight inhibitor bypassing activity; FVIII = factor VIII; ITI = immune tolerance induction; IU = international units; PE = pharmacoeconomic.

[a] Using an exchange rate from USD to CAD of 1.3103 at the moment of the review. Available from https://www.bloomberg.com/quote/USDCAD:CUR, accessed November 7th, 2018.

Source: Adapted from manufacturer's submission.[2]

The manufacturer included an additional scenario extending the use of emicizumab in the non-inhibitor populations. An epidemiology-based approach was taken using a three-year analysis time frame: reference year: 2018, year 1: 2019, year 2: 2020, year 3: 2021. A national perspective was applied; however, Quebec was excluded from the analysis.

As part of the review, the methods and assumptions of the manufacturer's budget impact analysis were assessed, and where possible, validated, and any further assessment of uncertainty considered in reanalyses. The manufacturer's base-case analysis estimates the number of patients with hemophilia A without inhibitors eligible for emicizumab prophylaxis over a three-year time horizon.

Table 18 summarizes the key model parameters used in the manufacturer's submission, and Figure 3 shows the market shares for the non-inhibitor population.

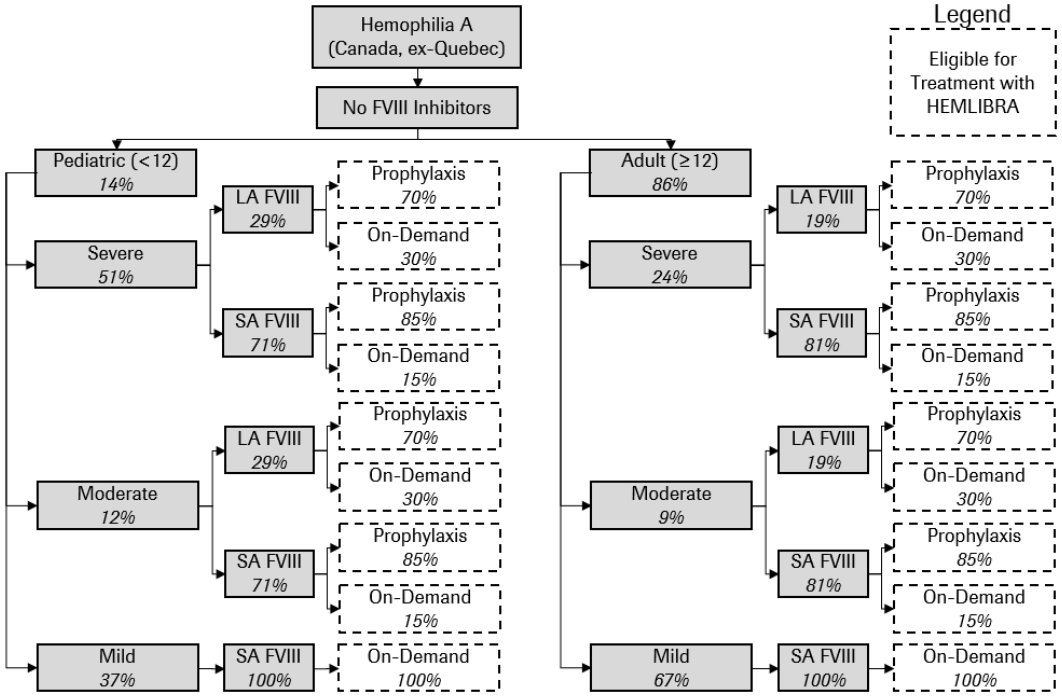
Table 18: Manufacturer's Regimen and Cost Inputs (Non-Inhibitor Population)

Parameter	Estimate		Source
	Pediatric	Adult	
Patient weight	[redacted]	[redacted]	Roche Australia study[12]
Treated Bleeds per Year			
Hemlibra	1.7	1.7	Oldenburg et al., Young et al.[27,28]
FVIII Prophylaxis	1.9	1.9	Oldenburg et al., Young et al.[27,28]
On-demand (Severe)	40.0	40.0	
On-demand (Moderate)	10.0	10.0	
On-demand (Mild)	4.0	4.0	
Dosage			
Hemlibra (Loading dose)	3.0 mg/kg q.w., weeks 1 to 4		Oldenburg et al., Young et al., product monograph[1,27,28]
Hemlibra (Maintenance dose)	1.5 mg/kg q.w., weeks 5+		Oldenburg et al., Young et al., product monograph[1,27,28]
Long-acting (Prophylaxis)	74.2 IU/kg/week		FEIBA monograph[29]
Long-acting (On-demand)	31.0 IU/kg/bleed		FEIBA monograph[29]
Short-acting (Prophylaxis)	76.2 IU/kg/bleed		Konkle et al.[14]
Short-acting (On-demand)	49.0 IU/kg/bleed		Niastase monograph[30]
Wastage			
Hemlibra	[redacted]	[redacted]	Roche data on file
Long-acting FVIII	[redacted]	[redacted]	Roche data on file
Short-acting FVIII	[redacted]	[redacted]	Roche data on file
Prices			
Hemlibra	[redacted]		Manufacturer's submission[2]
Long-acting FVIII	$1.8862/IU		PMPRB[17]
Short-acting FVIII	$1.2191/IU		PMPRB[17]
Proportion of severe hemophilia patients on a prophylactic regimen who would adopt emicizumab in years 1, 2, and 3	[redacted]		Assumption
Proportion of severe hemophilia patients on an on-demand regimen who would adopt emicizumab in years 1, 2, and 3	[redacted]		Assumption
Proportion of moderate hemophilia patients who would adopt emicizumab in years 1, 2,	[redacted]		Assumption

Parameter	Estimate		Source
	Pediatric	Adult	
and 3			
Proportion of mild hemophilia patients who would adopt emicizumab in years 1, 2, and 3	[redacted]		Assumption

FEIBA = factor eight inhibitor bypassing activity; FVIII = factor VIII; IU = international units; PMPRB = Patented Medicine Prices Review Board; q.w. = once weekly.

Figure 3: Non-Inhibitor Population Flow Diagram



FVII = factor VII; LA = long-acting ; SA = short-acting.

In addition to the assumptions detailed in Table 17, the following assumptions are required to estimate the budget impact analysis over the three-year period for the non-inhibitor population.

Table 19: Assumptions Used in Manufacturer's Budget Impact Analysis for the Non-Inhibitor Population and Revised in CADTH's Reanalyses

Manufacturer Base-Case Assumption (as Provided in its Budget Impact Analysis)	Additional CADTH Reanalyses
Annual treated bleeds derived from HAVEN 3 and HAVEN 4 studies.	None.
Wastage of dosage regimens for pediatric patients are [redacted] for emicizumab, long-acting FVIII, and short-acting FVIII, respectively. Wastage of dosage regimens for adult patients are [redacted], for emicizumab, long-acting FVIII, and short-acting FVIII, respectively.	None.
For the pediatric population, 51%, 12%, and 37% of the population have severe, moderate, and mild forms of hemophilia, respectively. For the adult population, 24%, 9%, and 67% of the population were severe, moderate, and mild, respectively.	The number of patients with hemophilia A was estimated from the most recent 2017 Canadian Hemophilia Registry report.[25] Data from the registry was divided into two groups by age to better match the HAVEN 1 and 2 study designs, in which a pediatric population was defined as patients younger than 12 years of age. Given that the Canadian Hemophilia Registry is divided into the following age groups (0 to 4, 5 to 9, 10 to 14, 15 to 24, 25 to 34, 35 to 44, 45 to 54, 55 to 64, 65 to 74, 75 to 84, and 85 and over), CADTH approximated the pediatric population as those patients younger than 15 years old and calculated the percentage of patients with hemophilia A by severity (patients with unknown and acquired hemophilia were excluded). Using this approach, 52%, 11%, and 37% of the pediatric population have severe, moderate, and mild hemophilia, respectively. Whereas 25%, 9%, and 66% of the adult population have severe, moderate, and mild hemophilia, respectively.
Market shares of comparator products Pediatric population: • 29% and 71% of severe patients are on long-acting and short-acting regimens, respectively. 70% of patients on long-acting regimens are on prophylaxis, whereas 85% of patients on short-acting regimens are on prophylaxis. • 29% and 71% of moderate patients are on long-acting and short-acting regimens, respectively. 70% of patients on long-acting regimen are on prophylaxis, and 85% of patients on short-acting regimens are on prophylaxis. Adult population: • 19% and 81% of severe patients are on long-acting and short-acting regimens, respectively. 70% of patients on long-acting regimens are on prophylaxis, whereas 85% of patients on short-acting regimens are on prophylaxis.19% and 81% of moderate patients are on long-acting and short-acting regimens, respectively. 70% of patients on long-acting regimens are on prophylaxis, whereas 85% of patients on short-acting regimens are on prophylaxis.	Based on revised market shares provided by CBS: Pediatric population: • [redacted] of severe patients are on long-acting and short-acting regimens, respectively, [redacted] of patients on long-acting regimens are on prophylaxis, whereas [redacted] of patients on short-acting regimens are on prophylaxis. • [redacted] of moderate patients are on long-acting and short-acting regimens, respectively. [redacted] of patients on long-acting regimen are on prophylaxis, and [redacted] of patients on short-acting regimens are on prophylaxis. Adult population: • [redacted] of severe patients are on long-acting and short-acting regimens, respectively. [redacted] of patients on long-acting regimens are on prophylaxis, whereas [redacted] of patients on short-acting regimens are on prophylaxis. • [redacted] of moderate patients are on long-acting and short-acting regimens, respectively. [redacted] of patients on long-acting regimens are on prophylaxis, whereas [redacted] of patients on short-acting regimens are on prophylaxis.
Kogenate was used as a proxy for short-acting FVIII, priced at $1.2191/IU, whereas Eloctate was used as a proxy for long-acting FVIII priced at $1.8862/IU	CBS provided actual unit pricing for short-acting and long-acting FVIII products. The products with the lowest available costs were used as proxies by CADTH. Xyntha was used as a proxy for short-acting FVIII, priced at $[redacted], whereas Adynovate was used as proxy for long-acting

Manufacturer Base-Case Assumption (as Provided in its Budget Impact Analysis)	Additional CADTH Reanalyses
	FVIII, priced at $[redacted][a] An additional analysis used the average cost of Xyntha and Kogenate as proxy for short-acting FVIII, at $[redacted], and the average cost of Adynovate and Eloctate as proxy for long-acting FVIII, at $[redacted]

CBS = Canadian Blood Services; FVIII = factor VIII; IU = international units.

[a] Using an exchange rate from USD to CAD of 1.3103 at the moment of the review. Available from https://www.bloomberg.com/quote/USDCAD:CUR, accessed November 7th, 2018.

Estimated Number of Treated Cases

The manufacturer estimated the total number of patients with hemophilia A from Statistics Canada actual and projected values9 and from the most recent report from the Canadian Hemophilia Registry.10 Table 20 details the estimated number of patients treated with BPA and emicizumab from 2018 to 2021, where emicizumab is and is not covered.

Table 20: Manufacturer's Estimate of Patient Numbers (Inhibitor)

	2018	2019	2020	2021
Without Emicizumab				
Pediatric				
FEIBA				
Prophylaxis	1	1	1	2
On-demand	–	–	–	–
Niastase				
Prophylaxis	1	1	1	1
On-demand	2	2	3	3
Pediatric total	**4**	**4**	**5**	**6**
Adult				
FEIBA				
Prophylaxis	24	25	27	29
On-demand	6	6	7	7
Niastase				
Prophylaxis	6	6	7	7
On-demand	14	15	16	17
Adult total	**50**	**52**	**57**	**60**
TOTAL	**54**	**56**	**62**	**66**
With Emicizumab				
Pediatric				
Emicizumab prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]
FEIBA				
Prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]
On-demand	[redacted]	[redacted]	[redacted]	[redacted]
Niastase				
Prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]
On-demand	[redacted]	[redacted]	[redacted]	[redacted]
Pediatric total	[redacted]	[redacted]	[redacted]	[redacted]
Adult				
Emicizumab prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]

	2018	2019	2020	2021
FEIBA				
Prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]
On-demand	[redacted]	[redacted]	[redacted]	[redacted]
Niastase				
Prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]
On-demand	[redacted]	[redacted]	[redacted]	[redacted]
Adult total	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL	[redacted]	[redacted]	[redacted]	[redacted]

FEIBA = factor eight inhibitor bypassing activity.

Source: Manufacturer's submission.[4]

Table 21 details the estimated number of patients who are non-inhibitor treated with short-acting and long-acting FVIII and emicizumab from 2018 to 2021, where emicizumab is and is not covered.

Table 21: Manufacturer's Estimate of Patient Numbers (Non-Inhibitor)

	2018	2019	2020	2021
Without Emicizumab				
Pediatric				
Severe				
Long-Acting FVIII				
Prophylaxis	36	38	40	44
On-demand	15	16	17	19
Short-Acting FVIII				
Prophylaxis	107	113	120	129
On-demand	19	20	21	23
Moderate				
Long-Acting FVIII				
Prophylaxis	8	9	9	10
On-demand	3	4	4	4
Short-Acting FVIII				
Prophylaxis	24	25	27	29
On-demand	4	5	5	5
Mild				
Long-Acting FVIII				
Prophylaxis	–	–	–	–
On-demand	–	–	–	–
Short-Acting FVIII				
Prophylaxis	–	–	–	–
On-demand	129	136	145	156
Pediatric total	345	366	388	419
Adult				
Severe				
Long-Acting FVIII				
Prophylaxis	70	73	78	84
On-demand	30	31	34	36
Short-Acting FVIII				

	2018	2019	2020	2021
Prophylaxis	362	382	407	438
On-demand	65	68	73	78
Moderate				
Long-Acting FVIII				
Prophylaxis	26	27	29	31
On-demand	11	12	12	13
Short-Acting FVIII				
Prophylaxis	135	142	152	163
On-demand	24	25	27	29
Mild				
Long-Acting FVIII				
Prophylaxis	–	–	–	–
On-demand	–	–	–	–
Short-Acting FVIII				
Prophylaxis	–	–	–	–
On-demand	1,473	1,555	1,657	1,784
Adult total	2,196	2,315	2,469	2,656
TOTAL	**2,541**	**2,681**	**2,857**	**3,075**
With Emicizumab				
Pediatric				
Emicizumab prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]
Severe				
Long-Acting FVIII				
Prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]
On-demand	[redacted]	[redacted]	[redacted]	[redacted]
Short-Acting FVIII				
Prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]
On-demand	[redacted]	[redacted]	[redacted]	[redacted]
Moderate				
Long-Acting FVIII				
Prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]
On-demand	[redacted]	[redacted]	[redacted]	[redacted]
Short-Acting FVIII				
Prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]
On-demand	[redacted]	[redacted]	[redacted]	[redacted]
Mild				
Long-Acting FVIII				
Prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]
On-demand	[redacted]	[redacted]	[redacted]	[redacted]
Short-Acting FVIII				
Prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]
On-demand	[redacted]	[redacted]	[redacted]	[redacted]
Pediatric total	[redacted]	[redacted]	[redacted]	[redacted]
Adult				
Emicizumab prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]
Severe				
Long-Acting FVIII				

	2018	2019	2020	2021
Prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]
On-demand	[redacted]	[redacted]	[redacted]	[redacted]
Short-Acting FVIII				
Prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]
On-demand	[redacted]	[redacted]	[redacted]	[redacted]
Moderate				
Long-Acting FVIII				
Prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]
On-demand	[redacted]	[redacted]	[redacted]	[redacted]
Short-Acting FVIII				
Prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]
On-demand	[redacted]	[redacted]	[redacted]	[redacted]
Mild				
Long-Acting FVIII				
Prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]
On-demand	[redacted]	[redacted]	[redacted]	[redacted]
Short-Acting FVIII				
Prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]
On-demand	[redacted]	[redacted]	[redacted]	[redacted]
Adult total	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL	[redacted]	[redacted]	[redacted]	[redacted]

FVIII = factor VIII.

Source: Manufacturer's submission.[2]

Manufacturer's Base Case

Table 22 to Table 29 summarize the approach taken by the manufacturer to calculate total costs in the reference treatment scenario and the new treatment scenario for pediatric and adult patients with inhibitors, respectively, in years 1 to 3.

Table 22: Total Costs for Pediatric Population With Inhibitors (Manufacturer's Analysis: Year 1)

	Reference Treatment Scenario		New Treatment Scenario		
	FEIBA	Niastase	Emicizumab Prophylaxis	FEIBA	Niastase
Pediatric population (N = 19)[a]					
Percentage of patients receiving treatment (A)	8%	17%	[redacted]	[redacted]	[redacted]
As prophylaxis (B)	80%	30%	[redacted]	[redacted]	[redacted]
As on-demand (C)	20%	70%	[redacted]	[redacted]	[redacted]
Cost of prophylaxis treatment (D = 19 x A x B x annual per-patient cost of prophylaxis)[b]	$632,222	$872,320	[redacted]	[redacted]	[redacted]
Cost of on-demand treatment (E = 19 x A x C x annual per-patient cost of on-demand treatment x number of bleeds per year)[b,c]	$0	$305,003	[redacted]	[redacted]	[redacted]
Total cost (D + E)	$632,222	$1,177,323	[redacted]	[redacted]	[redacted]

FEIBA = factor eight inhibitor bypassing activity.

[a] 75% of pediatric patients receive factor VIII therapy (i.e., 25% of patients on bypassing agents are likely candidates for emicizumab).

[b] The number of patients on prophylaxis (19 x A x B) and the number of patients on on-demand (19 x A x C) were rounded by the manufacturer.

[c] The number of annual bleeds is presented in Table 28.

[d] [redacted] of on-demand patients and [redacted] of bypassing agent prophylaxis patients assumed to switch to emicizumab, respectively [redacted] of patients will switch to emicizumab in year 1).

To summarize, based on prevalence data from the Canadian Hemophilia Registry,10 the manufacturer estimated that there will be 19 pediatric and 62 adult patients in Canada (excluding Quebec) in the first year after emicizumab coverage (2019). Of the 19 pediatric patients, one patient (19 x 8% x 80%) would be on FEIBA prophylaxis, no (19 x 8% x 20%) patients would be on FEIBA on-demand, two patients (19 x 17% x 70%) would be on Niastase on-demand, and one patient (19 x 17% x 30%) on Niastase prophylaxis. The remaining pediatric patients would receive FVIII therapy. In the new treatment scenario, [redacted] patients would receive emicizumab prophylaxis (19 x [redacted]) and [redacted] (19 x [redacted]) would receive Niastase on-demand, with the remaining patients receiving FVIII therapy. The total cost of each treatment was then calculated as the number of patients receiving each treatment by the annual cost per person. The annual cost per person is calculated as the sum of the annual treatment cost per person and the annual hospitalization and adverse event cost per person.

Table 23: Total Costs for Adult Population With Inhibitors (Manufacturer's Analysis: Year 1)

	Reference Treatment Scenario		New Treatment Scenario		
	FEIBA	Niastase	Emicizumab Prophylaxis	FEIBA	Niastase
Adult population (N = 62)					
Percentage of patients receiving treatment (A)[a]	51%	34%	[redacted]	[redacted]	[redacted]
As prophylaxis (B)	80%	30%	[redacted]	[redacted]	[redacted]
As on-demand (C)	20%	70%	[redacted]	[redacted]	[redacted]
Cost of prophylaxis treatment (D = 62 x A x B x annual per-patient cost of prophylaxis)[b]	$57,981,588	$19,278,228	[redacted]	[redacted]	[redacted]
Cost of on-demand treatment (E = 62 x A x C x annual per-patient cost of on-demand treatment x number of bleeds per year)[b,c]	$2,276,375	$6,832,645	[redacted]	[redacted]	[redacted]
Total cost (D + E)	$60,257,962	$26,110,873	[redacted]	[redacted]	[redacted]

FEIBA = factor eight inhibitor bypassing activity.

[a] 15% of adult patients receive factor VIII therapy (i.e., 85% of patients on bypassing agents are likely candidates for emicizumab).

[b] The number of patients on prophylaxis (62 x A x B) and the number of patients on on-demand (62 x A x C) were rounded by the manufacturer.

[c] Number of annual bleeds is presented in Table 29.

[d] [redacted] of on-demand patients and [redacted] of bypassing agent prophylaxis patients assumed to switch to emicizumab, respectively [redacted] of patients will switch to emicizumab in year 1).

Table 24: Total Costs for Pediatric Population With Inhibitors (Manufacturer's Analysis: Year 2)

	Reference Treatment Scenario		New Treatment Scenario		
	FEIBA	Niastase	Emicizumab prophylaxis	FEIBA	Niastase
Pediatric population (N = 22)[a]					
Percentage of patients receiving treatment (A)	8%	17%	[redacted]	[redacted]	[redacted]
As prophylaxis (B)	80%	30%	[redacted]	[redacted]	[redacted]
As on-demand (C)	20%	70%	[redacted]	[redacted]	[redacted]
Cost of prophylaxis treatment (D = 22 x A x B x annual per-patient cost of prophylaxis)[b]	$632,222	$872,320	[redacted]	[redacted]	[redacted]
Cost of on-demand treatment (E = 22 x A x C x annual per-patient cost of on-demand treatment x number of bleeds per year)[b,c]	$0	$457,505	[redacted]	[redacted]	[redacted]
Total cost (D + E)	$632,222	$1,329,825	[redacted]	[redacted]	[redacted]

FEIBA = factor eight inhibitor bypassing activity.

[a] 75% of pediatric patients receive factor VIII therapy (i.e., 25% of patients on bypassing agents are likely candidates for emicizumab).

[b] The number of patients on prophylaxis (22 x A x B) and the number of patients on on-demand (22 x A x C) were rounded by the manufacturer.

[c] Number of annual bleeds is presented in Table 28.

Table 25: Total Costs for Adult Population With Inhibitors (Manufacturer's Analysis: Year 2)

	Reference Treatment Scenario		New Treatment Scenario		
	FEIBA	Niastase	Emicizumab prophylaxis	FEIBA	Niastase
Adult population (N = 67)[a]					
Percentage of patients receiving treatment (A)	51%	34%	[redacted]	[redacted]	[redacted]
As prophylaxis (B)	80%	30%	[redacted]	[redacted]	[redacted]
As on-demand (C)	20%	70%	[redacted]	[redacted]	[redacted]
Cost of prophylaxis treatment (D = 67 x A x B x annual per-patient cost of prophylaxis)[b]	$62,620,115	$22,491,266	[redacted]	[redacted]	[redacted]
Cost of on-demand treatment (E = 67 x A x C x annual per-patient cost of on-demand treatment x number of bleeds per year)[b,c]	$2,655,770	$7,288,155	[redacted]	[redacted]	[redacted]
Total cost (D + E)	$65,275,885	$29,779,421	[redacted]	[redacted]	[redacted]

FEIBA = factor eight inhibitor bypassing activity.

[a] 15% of adult patients receive factor VIII therapy (i.e., 85% of patients on bypassing agents are likely candidates for emicizumab).

[b] The number of patients on prophylaxis (67 x A x B) and the number of patients on on-demand (67 x A x C) were rounded by the manufacturer.

[c] Number of annual bleeds is presented in Table 29.

Table 26: Total Costs for Pediatric Population With Inhibitors (Manufacturer's Analysis: Year 3)

	Reference Treatment Scenario		New Treatment Scenario		
	FEIBA	Niastase	Emicizumab prophylaxis	FEIBA	Niastase
Pediatric population (N = 24)[a]					
Percentage of patients receiving treatment (A)	8%	17%	[redacted]	[redacted]	[redacted]
As prophylaxis (B)	80%	30%	[redacted]	[redacted]	[redacted]
As on-demand (C)	20%	70%	[redacted]	[redacted]	[redacted]
Cost of prophylaxis treatment (D = 24 x A x B x annual per-patient cost of prophylaxis)[b]	$1,264,445	$872,320	[redacted]	[redacted]	[redacted]
Cost of on-demand treatment (E = 24 x A x C x annual per-patient cost of on-demand treatment x number of bleeds per year)[b,c]	$0	$457,505	[redacted]	[redacted]	[redacted]
Total cost (D + E)	$1,264,445	$1,329,825	[redacted]	[redacted]	[redacted]

FEIBA = factor eight inhibitor bypassing activity.

[a] 75% of pediatric patients receive factor VIII therapy (i.e., 25% of patients on bypassing agents are likely candidates for emicizumab).

[b] The number of patients on prophylaxis (24 x A x B) and the number of patients on on-demand (24 x A x C) were rounded by the manufacturer.

[c] Number of annual bleeds is presented in Table 28.

Table 27: Total Costs for Adult Population With Inhibitors (Manufacturer's Analysis: Year 3)

	Reference Treatment Scenario		New Treatment Scenario		
	FEIBA	Niastase	Emicizumab prophylaxis	FEIBA	Niastase
Adult population (N = 72)[a]					
Percentage of patients receiving treatment (A)	51%	34%	[redacted]	[redacted]	[redacted]
As prophylaxis (B)	80%	30%	[redacted]	[redacted]	[redacted]
As on-demand (C)	20%	70%	[redacted]	[redacted]	[redacted]
Cost of prophylaxis treatment (D = 72 x A x B x annual per-patient cost of prophylaxis)[b]	$67,258,642	$22,491,266	[redacted]	[redacted]	[redacted]
Cost of on-demand treatment (E = 72 x A x C x annual per-patient cost of on-demand treatment x number of bleeds per year)[c]	$2,655,770	$7,743,665	[redacted]	[redacted]	[redacted]
Total cost (D + E)	$69,914,412	$30,234,931	[redacted]	[redacted]	[redacted]

FEIBA = factor eight inhibitor bypassing activity.

[a] 15% of adult patients receive factor VIII therapy (i.e., 85% of patients on bypassing agents are likely candidates for emicizumab).

[b] The number of patients on prophylaxis (72 x A x B) and the number of patients on on-demand (72 x A x C) were rounded by the manufacturer.

[c] Number of annual bleeds is presented in Table 29.

Table 28: Costs for Pediatric Patients With Inhibitors

Product	Regimen	Number of Weeks in Regimen	Number of Bleeds per Regimen	Cost of Treatment per Week	Cost per Bleed	Annual Treatment Cost per Person	Annual Hospitalization and Adverse Event Costs per Person
Emicizumab	Prophylaxis	4 loading / 48.2 maintenance	0.2	[redacted]	[redacted]	[redacted]	$8,059
FEIBA	Prophylaxis	52.2	17.2	$9,988	$4,994	$607,083	$25,139
	On-demand		21.5		$4,994	$107,232	$21,592
Niastase	Prophylaxis	52.2	17.2	$14,226	$6,097	$847,181	$25,139
	On-demand		21.5		$6,097	$130,910	$21,592
FVIII	High-dose FVIII		21.5		$2,317	$49,752	$25,139
	ITI	52.2	5.4	$16,220	$4,994	$548,490	$25,139

FEIBA = factor eight inhibitor bypassing activity; FVIII = factor VIII; ITI = immune tolerance induction.

Note: Annual treatment cost per person = the number of bleeds per regimen X cost per bleed + number of weeks in regimen X cost of treatment per week.

Table 29: Cost for Adult Patients With Inhibitors

Product	Regimen	Number of Weeks in Regimen	Number of Bleeds per Regimen	Cost per Week	Cost per Bleed	Annual Treatment Cost per Person	Annual Hospitalization and Adverse Event Costs per Person
Emicizumab	Prophylaxis	4 loading / 48.2 maintenance	2.9	[redacted]	[redacted]	[redacted]	$8,059
FEIBA	Prophylaxis	52.2	14.9	$38,474	$19,237	$2,294,124	$25,139
	On-demand		18.6		$19,237	$357,804	$21,592
Niastase	Prophylaxis	52.2	14.9	$54,434	$23,329	$3,187,899	$25,139
	On-demand		18.6		$23,329	$433,918	$21,592
FVIII	High-dose FVIII		18.6		$8,934	$166,171	$25,139
	ITI	52.2	5.4	$19,237	$62,538	$2,114,642	$25,139

FEIBA = factor eight inhibitor bypassing activity; FVIII = factor VIII; ITI = immune tolerance induction.

Note: Annual treatment cost per person = number of bleeds per regimen X cost per bleed + number of weeks in regimen X cost of treatment per week.

Sensitivity analysis of the manufacturer's base case on the inhibitor population found that the three-year budget impact of introducing emicizumab ranged from savings of $13,840,003 to $167,896,857 (Table 30). None of the sensitivity scenarios resulted in a positive net incremental cost.

Table 30: Manufacturer's Sensitivity Analysis

	Incremental Budget Impact ($)			
	2019	2020	2021	Three-Year Total
Manufacturer's base case	–$31,295,993	–$40,705,147	–$48,991,658	–$120,992,798
Inhibitor prevalence from Webert et al.[32]	–$20,651,665	–$24,368,956	–$27,556,826	–$72,577,447
Inhibitor prevalence from Wight et al.[22]	–$47,044,395	–$56,669,841	–$64,182,621	–$167,896,857
Emicizumab market uptake is decreased to 50% over the base case for all BPA prophylaxis (no change to BPA on-demand)	–$25,646,954	–$28,699,565	–$30,015,640	–$84,362,159
Emicizumab market uptake is increased by 10% over the base case for all BPA regimens	–$35,530,748	–$45,667,911	–$54,241,765	–$135,440,425
Patient weight is decreased by 10%	–$28,203,134	–$36,682,217	–$44,157,364	–$109,042,714
Patient weight is increased by 10%	–$34,388,851	–$44,728,078	–$53,825,952	–$132,942,882
Efficacy is decreased to the 95% CI lower estimate for pediatric patients (annualized bleed rate of 0.1, 12.4, 18.4 for emicizumab, BPA prophylaxis, and on-demand treatment, respectively)[a]	–$31,242,163	–$40,647,694	–$48,908,125	–$120,797,982
Efficacy is increased to the 95% CI upper estimate for pediatric patients (annualized bleed rate of 0.8, 23.8, 35.3 for emicizumab, BPA prophylaxis, and on-demand treatment, respectively)[a]	–$31,369,944	–$40,795,230	–$49,123,143	–$121,288,317
No efficacy benefit from emicizumab for pediatric patients (annualized bleed rate of 0.2 for all treatments)	–$31,094,472	–$40,477,689	–$48,659,845	–$120,232,006

	Incremental Budget Impact ($)			
	2019	2020	2021	Three-Year Total
Efficacy is decreased to the 95% CI lower estimate for adult patients (annualized bleed rate of 1.7, 10.5, 15.2 for emicizumab, BPA prophylaxis, and on-demand treatment, respectively)[a]	–$30,129,910	–$39,166,683	–$47,098,639	–$116,395,232
Efficacy is increased to the 95% CI upper estimate for adult patients (annualized bleed rate of 5, 21.2, 22.8 for emicizumab, BPA prophylaxis, and on-demand treatment, respectively)[a]	-$32,776,213	-$42,645,065	-$51,365,581	- $126,786,859
No efficacy benefit from emicizumab for adult patients (annualized bleed rate of 2.9 for all treatments)	–$26,457,653	–$34,165,255	–$40,805,621	–$101,428,530
No wastage (perfect vial sharing)	–$31,072,613	–$40,402,250	–$48,646,093	–$120,120,957
Wastage is increased +2% over the base case	–$31,910,097	–$41,503,675	–$49,951,606	–$123,365,378
BPA/FVIII @ 30% disc. (vs. MAPP)	–$17,359,050	–$22,810,342	–$27,247,008	–$67,416,400
BPA/FVIII @ 40% disc. (vs. MAPP)	–$12,713,402	–$16,845,407	–$19,998,792	–$49,557,601
BPA/FVIII @ 50% disc. (vs. MAPP)	–$8,067,755	–$10,880,472	–$12,750,575	–$31,698,802
BPA/FVIII @ 60% disc. (vs. MAPP)	–$3,422,107	–$4,915,537	–$5,502,359	–$13,840,003
Exclude non-drug medical costs (drug/BPA/FVIII costs only)	–$30,928,588	–$40,229,306	–$48,342,943	–$119,500,837

BPA = bypassing agent; CI = confidence interval; disc. = discount; FVII = factor VII; MAPP = maximum average potential price; vs. = versus.

[a] Value could not be replicated.

Note: Negative values denote cost savings.

Source: Manufacturer's submission.[2]

CADTH was unable to replicate some of the efficacy scenario results reported in the manufacturer's report; however, given that the discrepancies were minimal (< 1% difference), CADTH did not consider this to be a significant issue. Values that could not be exactly replicated are specified in the table.

Table 31: Manufacturer's Results in the Non-Inhibitor Population (Excluding Non-Drug Medical Costs)

	Reference Scenario ($)			New Treatment Scenario ($)		
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
Pediatric	22,717,686	24,020,037	26,060,341	27,557,263	29,498,028	33,003,815
Adult	295,191,348	315,277,464	338,807,842	354,301,869	382,385,852	422,690,443
Total	317,909,034	339,297,501	364,868,183	381,859,132	411,883,880	455,694,259
Incremental cost[a]	Ref	Ref	Ref	63,950,098	72,586,379	90,826,076

Ref = reference.

[a] Incremental costs are calculated as the difference between the total costs in the new treatment scenario and the reference scenario.

Table 32: Manufacturer's Results in the Extended Population (Inhibitor and Non-Inhibitor)

	Reference Scenario ($)			New Treatment Scenario ($)		
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
Pediatric	40,685,912	43,299,775	47,272,030	43,617,613	46,639,951	51,401,613
Adult	447,348,051	479,594,735	512,434,148	473,669,533	503,866,031	544,840,678
Total	488,033,963	522,894,510	559,706,179	517,287,146	550,505,982	596,242,290
Incremental cost[a]	Ref	Ref	Ref	29,253,183	27,611,472	36,536,112

Ref = reference.

[a] Incremental costs are calculated as the difference between the total costs in the new treatment scenario and the reference scenario.

CADTH Reanalysis

Base-Case Analysis

Table 33: CADTH Estimate of Budget Impact in the Inhibitor Population

		2019	2020	2021	Three-Year Total
	Manufacturer base case	–$31,295,993	–$40,705,147	–$48,991,658	–$120,992,798
1	ABR value for on-demand BPA patients based on HAVEN 1	–$31,408,659	–$40,953,794	–$49,381,075	–$121,743,527
2	Number of patients with hemophilia A and proportion with inhibitors based on 2017 estimates	–$22,402,212	–$28,069,164	–$33,412,081	–$83,883,457
3	Revised uptake rate of emicizumab	–$43,428,183	–$50,737,129	–$54,030,824	–$148,196,136
4	Revised CBS market shares for BPA	–$27,913,418	–$29,742,707	–$31,225,754	–$ 88,881,879
5	Revised CBS BPA unit costs	–$39,372,229	–$43,284,672	–$45,761,954	–$128,418,854
6	**CADTH base case (1 to 5)**	**–$32,920,731**	**–$34,750,021**	**–$36,545,226**	**–$104,215,978**
6a	Body weight 30% less than base case	–$23,228,991	–$24,508,584	–$25,771,789	–$73,509,364
	Body weight 30% more than base case	–$42,596,844	–$44,974,920	–$47,301,145	–$134,872,909
6b	Body weight equal to average UK-based body weight	–$33,968,488	–$35,851,636	–$37,674,790	–$107,494,913
6c	Number of treated bleeds per year based on data provided by CBS from CBDR	–$29,440,271	–$31,269,561	–$32,913,829	–$93,623,661
6d	No waste of emicizumab or BPA	–$32,795,063	–$34,556,399	–$36,340,350	–$103,691,812
6e	Excluding non-drug medical costs	–$32,253,708	–$34,082,997	–$35,853,064	–$102,189,769

ABR = estimate annual bleeding rate; BPA = bypassing agent; CBDR = Canadian Bleeding Disorders Registry; CBS = Canadian Blood Services.

Note: Negative values denote cost savings.

Table 34: CADTH Scenario Analysis in the Extended Population (Inhibitor and Non-Inhibitor)[a]

	Reference Scenario ($)			New Treatment Scenario ($)_		
Including Drug and Non-Drug (Hospitalization and Adverse Event) Costs						
	Year 1	**Year 2**	**Year 3**	**Year 1**	**Year 2**	**Year 3**
Pediatric	20,509,923	20,794,631	21,180,708	51,261,939	49,254,210	50,773,495
Adult	149,722,835	152,128,055	159,549,814	553,124,866	532,293,783	554,217,098
Total	170,232,759	172,922,687	180,730,521	604,386,805	581,547,993	604,990,593
Incremental cost[b]	Ref	Ref	Ref	434,154,046	408,625,306	424,260,072
Including Drug Costs Only						
	Year 1	**Year 2**	**Year 3**	**Year 1**	**Year 2**	**Year 3**
Pediatric	20,003,286	20,287,994	20,674,071	50,959,600	48,951,872	50,471,156
Adult	148,687,664	151,092,884	158,464,364	552,552,420	531,721,336	553,619,513
Total	168,690,950	171,380,878	179,138,435	603,512,020	580,673,208	604,090,669
Incremental cost[b]	Ref	Ref	Ref	434,821,070	409,292,330	424,952,234

Ref = reference.

[a] Assuming 100% uptake rate in both inhibitor and non-inhibitor populations (other assumptions in line with CADTH base case).

[b] Incremental costs are calculated.

Jurisdictional Budget Impact

CADTH attempted to estimate the proportion of emicizumab costs that would be borne within each province and territory, excluding Quebec, by multiplying the total projected budget by the proportion of the national population residing within each jurisdiction. Budget impact can be found in Table 35. This analysis assumes the prevalence of hemophilia A and hemophilia with inhibitors are the same across jurisdictions in Canada; however, actual differences in prevalence among jurisdictions are unknown.

Table 35: CADTH's Estimated Budget Impact of Reimbursing Emicizumab by Jurisdiction

Jurisdiction	Estimated Population 2018	Proportion of National Population	Cost in the Inhibitor Population ($)			Cost in the Non-Inhibitor Population ($)			Cost in the Extended Population (Inhibitor and Non-Inhibitor) ($)		
			Year 1, 2019	Year 2, 2020	Year 3, 2021	Year 1, 2019	Year 2, 2020	Year 3, 2021	Year 1, 2019	Year 2, 2020	Year 3, 2021
Canada, excluding Quebec	28,557,550	100.00%	-32,920,731	-34,750,021	-36,545,226	76,431,845	90,122,437	110,764,370	43,511,114	55,372,417	74,219,144
Newfoundland and Labrador	533,365	1.87%	-614,855	-649,021	-682,549	1,427,505	1,683,202	2,068,729	812,650	1,034,182	1,386,179
Prince Edward Island	153,328	0.54%	-176,755	-186,576	-196,215	410,370	483,877	594,705	233,616	297,300	398,490
Nova Scotia	962,072	3.37%	-1,109,063	-1,170,690	-1,231,168	2,574,904	3,036,125	3,731,529	1,465,841	1,865,435	2,500,361
New Brunswick	766,188	2.68%	-883,250	-932,330	-980,494	2,050,637	2,417,950	2,971,765	1,167,386	1,485,621	1,991,271
Ontario	14,315,447	50.13%	-16,502,641	-17,419,635	-18,319,543	38,314,073	45,176,949	55,524,423	21,811,432	27,757,315	37,204,880
Manitoba	1,349,617	4.73%	-1,555,819	-1,642,270	-1,727,111	3,612,134	4,259,145	5,234,673	2,056,315	2,616,875	3,507,563
Saskatchewan	1,173,935	4.11%	-1,353,295	-1,428,493	-1,502,290	3,141,936	3,704,725	4,553,267	1,788,641	2,276,232	3,050,977
Alberta	4,322,995	15.14%	-4,983,486	-5,260,401	-5,532,156	11,570,127	13,642,586	16,767,327	6,586,641	8,382,185	11,235,171
British Columbia	4,858,588	17.01%	-5,600,910	-5,912,133	-6,217,557	13,003,595	15,332,819	18,844,698	7,402,685	9,420,687	12,627,141
Yukon	38,790	0.14%	-44,716	-47,201	-49,639	103,817	122,413	150,451	73,026	91,845	121,532
Northwest Territories	44,903	0.16%	-51,763	-54,640	-57,462	$120,179	$141,705	$174,162	84,534	106,320	140,685
Nunavut	38,323	0.13%	-44,178	-46,633	-49,042	$102,568	$120,940	$148,640	72,146	90,739	120,069

Note: National population excludes that of Quebec.

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