CADTH

CADTH TECHNOLOGY REVIEW

Drug Therapies for the Long-Term Prophylaxis of Hereditary Angioedema Attacks

Service Line:	Health Technology Assessment
Issue:	25
Publication Date:	December 2019
Report Length:	92 Pages

CADTH

Authors: Michel Boucher, Stephanie Chiu, Mina Tadrous, Estefania Ruiz-Vargas, Tessa Cornelissen, David Kaunelis, Robyn Butcher

Cite As: *Drug Therapies for the Long-Term Prophylaxis of Hereditary Angioedema Attacks*. Ottawa: CADTH; 2019 Dec. (CADTH Technology Review; no. 25).

Acknowledgments:

ISSN: 2369-7377

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.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

CADTH

Table of Contents

Tables

Figures

Abbreviations

BIA	budget impact analysis
CBS	Canadian Blood Services
C1-INH	C1-esterase inhibitor
C1-INH HAE	hereditary angioedema due to C1-INH deficiency
C1-INH HAE 1	C1-INH HAE type 1
C1-INH HAE 2	C1-INH HAE type 2
HAE-nC1INH	HAE with normal C1 function
HAE	hereditary angioedema
ICER	Institute for Clinical and Economic Review
ICUR	incremental cost-utility ratio
IV	intravenous
LTP	long-term prophylaxis
MSAC	Australian Medical Services Advisory Committee
NHS	National Health Service
QALY	quality-adjusted life-year
SC	subcutaneous
WTP	willingness to pay

Executive Summary

Rationale and Policy Issues

Hereditary angioedema (HAE) is a rare disorder with an estimated prevalence of one in 50,000. In most cases, it is an autosomal dominant disorder caused by mutations in the SERPING gene that results in C1-esterase inhibitor (C1-INH) deficiency. Individuals with this condition have unpredictable attacks of painful swelling typically affecting the extremities, bowel mucosa, genitals, face, and upper airway. These attacks may have a significant impact on patients, as they may decrease an individual's ability to function normally and may reduce their health-related quality of life. Death can occur in cases of laryngeal involvement. There are three different types of HAE:

- Type 1, which is associated with low antigenic and functional levels of C1-INH (C1-INH HAE 1). This type is the most prevalent, accounting for 85% of cases.[1]
- Type 2 is associated with normal C1-INH levels and impaired C1-INH function (C1-INH HAE 2). This type accounts for 15% of cases.[1]
- HAE with normal C1-INH function (HAE-nC1INH; formerly referred to as type 3), which is much less prevalent.

It is generally acknowledged that C1-INH HAE management involves three key approaches:

- treatment of acute attacks (on-demand therapy), which aims to reduce the duration and severity of acute attacks
- short-term prophylaxis, which aims to reduce the risk of acute attacks when there may be an increased risk of having such attacks (e.g., during medical or dental interventions)
- long-term prophylaxis (LTP), which involves initiating continuous regular treatment aimed at minimizing the number, frequency, and severity of attacks when on-demand treatment does not sufficiently meet patient treatment requirements.[1]

Drugs available in Canada for the treatment of acute and LTP HAE attacks are listed in Table 1.

Injection of C1-INH concentrate products (e.g., Berinert) or icatibant at the onset of HAE attacks is the usual approach for on-demand therapy. For LTP, C1-INH concentrate products are also commonly used. Cinryze and Haegarda both have a Health Canada indication for LTP, but Haegarda has not been widely available. Berinert is also used for LTP (either via an intravenous [IV] or subcutaneous [SC] route of administration). An additional option is lanadelumab, a monoclonal antibody for SC administration. Although available for oral administration, use of danazol and tranexamic acid appears to be declining in Canada due to their limited efficacy and adverse effect profiles.

Table 1: Injectable Products Available in Canada for Hereditary Angioedema Due to C1-Esterase Inhibitor Deficiency

Product Name (Brand Name)	Product Source	Route of Administration
Treatment of Acute HAE Attacks (On-Demand Therapy)		
C1-INH concentrate – human (Berinert)	Plasma-derived	IV
Icatibant acetate (Firazyr)	Synthetic peptidomimetic	SC[a]
Long-Term Prophylaxis of C1-INH HAE Attacks		
C1-INH concentrate – human (Cinryze)	Plasma-derived	IV
C1-INH concentrate – human (Haegarda)[b]	Plasma-derived	SC
Lanadelumab (Takhzyro)	Human monoclonal antibody	SC

C1-INH = C1-esterase inhibitor; HAE = hereditary angioedema; IV = intravenous injection; SC = subcutaneous injection.

[a] Pre-filled syringe for slow subcutaneous injection.

[b] Product approved but not yet marketed in Canada.

The purpose of this report is to inform policy decisions on plasma-derived C1-INH concentrate and non-plasma–derived products used in Canada for LTP of C1-INH HAE attacks. It has been observed that the utilization and reimbursement costs for C1-INH concentrate products for the treatment and prophylaxis of C1-INH HAE attacks have increased substantially over recent years. Based on this observation, the policy issue faced by Canadian jurisdictions centres around determining how best to fund C1-INH concentrate and non-plasma–derived products so that patients who are deriving benefit from these products for LTP of C1-INH HAE attacks continue to have access to these therapies, while ensuring such utilization represents an efficient use of health care resources. Two policy questions were developed to characterize this issue:

Policy Questions

1) What is the optimal use of available C1-INH concentrate and non-plasma–derived products for the LTP of C1-INH HAE attacks in Canada?
2) What are the implications of alternative policies for reimbursement of C1-INH concentrate and non-plasma–derived products for LTP of C1-INH HAE attacks in Canada?

Methods

In order to address the two policy questions, this report includes four components. Each of these components aims to answer the following specific research questions:

Clinical expert consultation

1) How is LTP of C1-INH HAE attacks currently managed in Canadian clinical practice?
2) What are the characteristics of patients who are most likely to benefit from C1-INH concentrate and non-plasma–derived products for the LTP of C1-INH HAE attacks?
3) How might patients who are most likely to benefit from LTP of C1-INH HAE attacks be identified?

Utilization Analysis

1) What are the current utilization patterns of C1-INH concentrate products in Canada for the LTP of C1-INH HAE attacks?

2) What are the costs associated with this utilization?

Cost-Utility Analysis

1) What is the comparative cost-effectiveness of available C1-INH concentrate and non-plasma–derived products in Canada for LTP versus no LTP of C1-INH HAE attacks?

Budget Impact Analysis

1) What is the budget impact of providing LTP for patients with HAE in Canada?

Report Components

Methodology was developed for each of the four report components in order to answer the related research questions; a brief description for each component follows.

Clinical expert consultation: A panel of four clinical experts from Ontario with expertise in the diagnosis and management of C1-INH HAE in Canada was convened by CADTH for this consultation. The role of the expert panel was to elucidate the following:

- how LTP for the prevention of HAE attacks is currently used in Canadian clinical practice
- the characteristics of the patients who are most likely to benefit from LTP with C1-INH or lanadelumab to prevent HAE attacks
- how such patients are identified in Canadian clinical practice.

A list of questions was provided to the experts for this consultation. A summary of the panellists' responses was prepared by CADTH staff after the consultation, which was then validated by all panel members.

Utilization analysis: A drug-utilization analysis of C1-INH concentrate products distributed nationally between October 1, 2009 and March 31, 2019 was conducted. To conduct this analysis, data supplied by Canadian Blood Services (CBS) on product distribution were used. Data were available for two products used as LTP for the prevention of C1-INH HAE attacks which were included in the analysis, i.e., Berinert and Cinryze. These data reported the total number of units distributed to blood banks by calendar quarter and their associated cost per quarter. A supplementary analysis was also performed using user-level data received from the British Columbia Provincial Health Services Authority.

Economic evaluation: Based on a review of recently conducted economic evaluations, CADTH identified a study conducted by the Institute for Clinical and Economic Review (ICER) in the US on the effectiveness and value of LTP of HAE with lanadelumab and C1-INH concentrate products. To leverage the research already conducted, CADTH obtained a copy of the model used in the ICER analysis (as developed by researchers at the University of Washington) and adapted the model to address the specific research question. The model was used to assess the lifetime costs, health outcomes, and cost-effectiveness of LTP of HAE attacks compared with no LTP (i.e., patients only receive on-demand therapies for the treatment of acute attacks). On-demand treatment for acute attacks consisted of treatment with the following drugs approved in Canada: Berinert and icatibant, whereas LTP

consisted of the following drugs: Cinryze, lanadelumab, and Berinert. Haegarda was included in a scenario analysis, as it is not currently marketed in Canada.

The model was based on two health states: alive with C1-INH HAE and dead. All patients in the model started in the alive state and could experience attack events or death during each monthly cycle; the risk of these events depended on the LTP treatment received. All patients on LTP were assumed to have access to on-demand treatment for acute attacks, and LTP therapies were assumed to be taken on a lifelong basis. A complete description of the model can be found in the ICER report.[2] Details on the model structure and model parameter values, as well as the changes made to the model by CADTH, can be found in Appendix 1. Briefly, only therapies approved in Canada were included in the analysis; the discount rate was set to 1.5% as per Canadian guidelines;[3] and Canadian administration, monitoring, and drug costs were used in the model. Results were based on probabilistic analysis. Pairwise incremental cost-utility ratios (ICURs) were calculated for each LTP therapy versus no LTP, as were sequential ICURs for all LTP therapies. Probabilistic scenario analyses were conducted where relevant, and included alternative costs for Haegarda, alternative monthly attack rates and alternative dosing for lanadelumab.

Budget impact analysis (BIA): CADTH developed a BIA to estimate the financial impact of new therapies for C1-INH HAE as well as the financial impact of providing LTP compared with no LTP. The BIA was built using a prevalence-based approach from the perspective of the Canadian publicly funded payer over a three-year time horizon (considering drug costs only). The primary analysis compared two scenarios: a reference scenario, where only therapies currently used for LTP were included (Berinert and Cinryze), and a new-drug scenario, where Haegarda and lanadelumab become accessible to patients. Exploratory analyses were also conducted to examine the budget impact of providing prophylaxis by comparing two scenarios: a reference scenario, where patients are treated with on-demand therapies only and do not receive prophylaxis, and a prophylaxis scenario where patients requiring prophylaxis receive treatment with currently available therapies (Berinert and Cinryze).

Results

Clinical expert consultation: Input from the panel of four clinical experts gathered for this project provided an opportunity to understand the perspective of clinicians caring for patients with C1-INH HAE. A few key conclusions can be made from this consultation:

- LTP is an important component of the overall management of patients with C1-INH HAE, and many patients with HAE are using LTP treatment.
- Use of C1-INH concentrate currently appears to be a preferred option for LTP of acute attacks compared with oral LTP. As new drugs become available, use of oral therapies (danazol and tranexamic acid) is expected to decline over time, as these interventions are considered less effective and are not well tolerated by many patents.
- Route of administration, dosing frequency, and perceived risk of infection may affect choice of LTP treatment. Currently, many drugs available for LTP of C1-INH HAE attacks are injectable. In this context, drugs administered subcutaneously are generally preferred over the use of IV drugs. To that effect, the panellists anticipated that the availability of new therapies intended for SC administration (e.g., Haegarda and lanadelumab) would increase the proportion of patients with HAE receiving LTP, although the amount of increase was difficult for the panellists to predict. Further, lanadelumab has a less frequent dosing schedule, which will likely be considered more convenient.

- The impact of LTP on the frequency and severity of C1-INH HAE attacks alone does not fully capture the effect of these therapies. It is also important to consider the impact of these attacks on patients' health-related quality of life and their ability to maintain or resume normal activities.
- Key characteristics of patients who may be considered for LTP of C1-INH HAE attacks would generally include: a confirmed diagnosis of C1-INH HAE 1 or C1-INH HAE 2 (there is a lack of evidence supporting the use of C1-INH prophylaxis in patients with HAE-nC1INH), a higher frequency of attacks and, importantly, the presence of severe attacks, such as those that could be debilitating to patients or life-threatening (e.g., attacks with laryngeal involvement).
- There was consensus among the clinical experts that patients should not be required to try oral LTP therapies before gaining access to C1-INH concentrate or monoclonal antibodies.

Overall, the experts agreed that LTP of C1-INH HAE attacks adds clinical value to the treatment landscape by allowing patients to live a normal life: to work, go to school, perform daily activities, and to participate in recreational and social activities.

The key results from the clinical expert consultation regarding choice of therapy for LTP align with updated recommendations in the recently published 2019 International/Canadian Hereditary Angioedema Guideline.[4] As mentioned previously, SC administration of C1-INH concentrate or lanadelumab was considered by the panel to be more feasible than IV administration of C1-INH concentrate, which is consistent with the 2019 guideline recommendation that SC C1-INH concentrate or lanadelumab should be used as first-line therapy for LTP in patients with C1-INH HAE 1 and C1-INH HAE 2. The recommendation may also support the panel's expectation that increased availability of lanadelumab and Haegarda may increase the proportion of patients with HAE who receive LTP.

The key characteristics of patients who may be considered for LTP of C1-INH HAE attacks remained broadly defined by the panellists, who were not able to identify an attack threshold for initiating LTP that could be applied to all patients with HAE. Thresholds identified in recommendations issued for LTP therapies by public-funding organizations vary and may reflect differences in the factors taken into consideration for the recommendations. For example, the lanadelumab recommendation issued by the CADTH Canadian Drug Expert Committee includes a threshold of at least three HAE attacks within a four-week period, which was consistent with the mean baseline attack frequencies observed in the main clinical trial for lanadelumab. In contrast, recommendations in two other countries specify thresholds of at least two clinically significant attacks per week or at least eight attacks per month.

Utilization analysis: Over the 10-year observational period, the total number of C1-INH concentrate units distributed by CBS per quarter increased 18-fold from 679,000 units in the fourth quarter of 2009 (Q4 2009) to 12,444,000 units in Q2 2019. Of the two C1-INH concentrate products used in 2018, Berinert was the most distributed nationally, representing 98% (47 million units) of the total units distributed compared with 2% (0.8 million units) for Cinryze. On average, year-to-year utilization grew 36% over that time. The utilization of these products was forecasted to continue growing in 2020, with projected growth to [redacted] units of Berinert and [redacted] units of Cinryze; this represents an increase of [redacted] for Berinert and [redacted] for Cinryze.

Similar trends were observed for total spending over the same 10-year observation period. The total cost of C1-INH concentrate units distributed per quarter increased 24-fold from $915,000 in Q4 2009 to $22,370,000 in Q2 2019. Berinert accounted for [redacted] of total expenditures in 2018 compared with only [redacted] for Cinryze. On average, total spending on C1-INH concentrate grew 43% annually during that time. Based on this continued growth, it was forecasted that, by 2020, spending will grow to [redacted] for Berinert and remain around [redacted] for Cinryze, a growth of 35% for Berinert and 18% for Cinryze. The observed difference in national utilization growth over time compared with total spending can likely be accounted for by changes in the cost per unit of product.

A greater than three-fold difference in C1-INH distribution was observed between the jurisdictions; the highest utilization rate occurred in Nova Scotia (3,592 units per 1,000 people) while the lowest utilization rate was observed in British Columbia (1,127 units per 1,000 people). Similar observations were made for spending, with the highest rate occurring in Nova Scotia ($6,240 per 1,000 people) and the lowest in British Columbia ($1,958 per 1,000 people). Although the spending rate was not the highest, the largest proportions of units were distributed to Ontario (47%; 22,488,000 units) and Alberta (18%; 8,616,500 units), accounting for nearly two-thirds of all units distributed.

Economic evaluation: In the base-case sequential analysis, Cinryze was associated with an ICUR of $673,632 per quality-adjusted life-year (QALY) compared with no LTP, whereas lanadelumab was associated with an ICUR of $12,992,477 per QALY compared with Cinryze. Berinert was dominated by lanadelumab, which means lanadelumab was associated with lower total costs and higher QALYs compared with Berinert. Additionally, lanadelumab had an ICUR of $5,275,949 per QALY compared with no LTP, whereas Berinert had an ICUR of $9,919,626 compared with no LTP. Lanadelumab and Berinert had a 0% probability of being cost-effective versus no LTP at a willingness-to-pay (WTP) threshold of $50,000 to $150,000 per QALY gained, whereas Cinryze had a small probability (2%) of being cost-effective at a WTP threshold of $50,000 per QALY gained. Cinryze, lanadelumab, and Berinert would require a price reduction of 70%, 82%, and 87%, respectively, to be cost-effective at a conventionally accepted WTP threshold of $50,000.

If Haegarda is marketed in Canada at the price submitted by CBS, then Haegarda would be dominated by lanadelumab, which means lanadelumab would be associated with lower total costs and higher QALYs compared with Haegarda. However, if Haegarda is marketed at the same price as Cinryze (the lowest-cost LTP treatment), then Haegarda would become the lowest-cost treatment and would be associated with lower cost and higher QALYs compared with no LTP and Cinryze (i.e., Haegarda would dominate no LTP and Cinryze). The model results were most sensitive to attack duration. If all treated attacks take 48 hours to resolve when treated, and untreated attacks take 72 hours to subside, then the ICUR for Cinryze versus no LTP decreases to $284,233 per QALY, whereas the ICUR for lanadelumab versus Cinryze decreases to $9,470,001 per QALY.

Since the costs related to lost wages and out-of-pocket expenses for patients experiencing acute attacks are small relative to the total health care costs of managing C1-INH HAE, considering a societal perspective (including direct health care costs and indirect patient costs) resulted in ICURs similar to those in the base-case analysis.

BIA: For the reference scenario, the current budget impact of C1-INH concentrate and icatibant is estimated to be $81,861,027 annually and $245,043,080 over three years. Compared with the reference scenario, introducing new LTP therapies (Haegarda and lanadelumab) will result in estimated cost savings of $18,506,975 over three years. Results of the sensitivity analyses demonstrate that, in all scenarios, unless all patients are currently

using Berinert subcutaneously at a lower dose, introducing new therapies appears to be a cost saving relative to the current treatment paradigm. In the current treatment paradigm, where Berinert and Cinryze are the only treatments used for LTP, the budget impact of providing LTP compared with not providing LTP is estimated to be $56,882,033 annually or $170,646,098 over three years. Results of the sensitivity analyses demonstrate that for all scenarios explored, providing prophylaxis is never a cost saving compared with not providing prophylaxis. Providing LTP becomes less costly in scenarios where patients requiring LTP have higher baseline attack frequencies.

Limitations

Clinical expert consultation: The main limitation associated with the clinical expert consultation is that all of the participating experts were located in Ontario. Therefore, the expert opinion summarized in this report may be limited to clinical practice in Ontario and may not reflect clinical practice in other Canadian jurisdictions. However, given that C1-INH HAE is a rare condition, the number of Canadian physicians considered to be experts in this condition is limited, and it is unlikely that current clinical practice differs dramatically across Canada. Characteristics of patients who may be considered for LTP of C1-INH HAE attacks remained broadly defined and the experts did not identify a specific threshold for attack frequency that would warrant consideration of LTP.

Utilization analysis: The key limitation of the utilization analysis is that the data source only included aggregate distribution volumes of Berinert and Cinryze without clinical information such as associated indications or patient information (e.g., age, sex). Therefore, it was not possible to attribute utilization of either product to the actual reason for clinical use (i.e., treatment of acute C1-INH HAE attacks or LTP for these attacks). This precluded the ability to conduct an analysis of the appropriateness or changing modalities of use for these plasma-derived products. Another limitation is that the analysis only included two products, Berinert and Cinryze, whereas lanadelumab is also approved for LTP of HAE attacks; however, at the time this analysis was conducted, public reimbursement of lanadelumab was not yet available.

Economic evaluation: Evidence on the long-term effectiveness of LTP treatments is not available due to the short duration of clinical trials. This limitation increases the uncertainty in the long-term management of patients with C1-INH HAE. Furthermore, in the clinical setting, it has been observed that some patients using LTP may tend to extend the dosing intervals of their LTP treatment beyond what is stipulated on the product label. This tendency usually reflects patients' desire to minimize the number of injections they give themselves and tailor their LTP treatment to the pattern of their condition. These utilization patterns are not reflected in the model. The clinical expert consulted by CADTH noted that abdominal attacks could also be fatal; however, abdominal attacks are not included in the model and, as such, this remains a limitation of the analysis. Finally, due to the lack of US- and Canada-specific data on utilities, estimates from a study in Sweden were used instead.

BIA: There is a paucity of data regarding the prevalence of C1-INH HAE in Canada. Additionally, the number of patients diagnosed with this condition who are being treated and are receiving LTP are also unknown. As the results of the BIA are very sensitive to the number of patients considered, further research to more accurately capture the number of patients using these products and for what indication (LTP or on-demand therapy) would provide more reliable estimates of the financial impact. In addition, should Haegarda and lanadelumab become accessible to patients, their uptake is unknown. A further limitation is that the BIA only considered the influence of LTP on attack frequency, not attack severity. In

the scenario where no LTP is provided, on-demand therapy costs may be higher than predicted by the BIA if LTP also reduces attack severity. Finally, the BIA assumed that all patients requiring LTP had the same attack frequency when, in reality, patients requiring such prophylactic therapy will likely have a wide distribution of attack frequency and severity, which the BIA was unable to capture.

Conclusions and Implications for Decision- or Policy-Making

The use of LTP to prevent acute HAE attacks is recognized as an important treatment option for patients with C1-INH HAE, as these treatments have the potential to reduce the frequency of HAE attacks and improve patient health-related quality of life. Patients with frequent and severe attacks, particularly if associated with significant morbidity and reduction in daily function, would be expected to benefit most from LTP therapies. The utilization of these products is sharply increasing in Canada and, at their current prices, none of the therapies intended for LTP are cost-effective. This increased utilization, combined with the high prices of products for LTP of C1-INH HAE attacks, has considerable budgetary implications for public payers. Careful selection of patients and a substantial reduction in the price of these products would be avenues to be considered to ensure the sustainability of access to these therapies in Canada.

Introduction

Clinical and Technology Background

Hereditary angioedema (HAE) is an autosomal dominant disorder.[1,5] In most cases, this condition results from mutations in the *SERPING1* gene, which is associated with deficiency in the quantity or function of C1-esterase inhibitor (C1-INH).[5] This deficiency leads to overproduction of bradykinin, a potent vasoactive peptide. Bradykinin production is associated with increased vascular permeability and vasodilation as well as extravasation of fluid into subcutaneous tissues.[6] These cause edema of subcutaneous tissues, submucosa of the gastrointestinal, genitourinary, and upper respiratory tracts.[5] For this reason, patients with this condition have unpredictable attacks of painful swelling typically affecting the extremities, bowel mucosa, genitals, face, and upper airway. These attacks may have significant impact for patients, as they may decrease their ability to function normally and reduce their quality of life. Death can occur in cases of laryngeal involvement.[1]

The prevalence of HAE due to C1-INH deficiency (C1-INH HAE) is approximately 1:50,000;[1] recent estimates from European population-based epidemiological studies suggest that the prevalence of diagnosed cases of this condition may be somewhat less, i.e., approximately 1:67,000.[6] Of note, there are three different types of HAE:[1]

- Type 1 is associated with low antigenic and functional levels of C1-INH (C1-INH HAE 1). C4 levels are typically reduced. This type represents about 85% of HAE cases.
- Type 2 is associated with normal C1-INH levels but impaired C1-INH function (C1-INH HAE 2). As is the case for C1-INH HAE 1, C4 levels are also typically reduced in C1-INH HAE 2. This type accounts for about 15% of HAE cases.
- HAE with normal C1-INH function (HAE-nC1INH; formerly referred to as type 3) is much less prevalent. Its true prevalence is unknown, as there are no reliable assays to screen for this condition.

Evidence indicates that when C1-INH blood levels are below a certain threshold, either because of a quantitative deficiency of C1-INH (i.e., C1-INH HAE 1) or dysfunctional C1-INH (i.e., C1-INH HAE 2), the risk of attack increases. This observation provides the rationale for C1-INH replacement therapy, which may be administered intravenously or subcutaneously and aims to restore the concentration and functional activity of C1-INH, regulate the release of bradykinin, and attenuate or prevent subcutaneous (SC) and submucosal edema associated with C1-INH HAE 1 and C1-INH HAE 1.[5]

It is generally acknowledged that C1-INH HAE management involves three key approaches:

- Treatment of acute attacks (on-demand therapy): This approach aims to reduce the duration and severity of attacks to minimize the impact of these on the functional ability of the patient as well as to reduce the related morbidity and potential mortality. Prompt administration of on-demand therapies is essential, in addition to preparing for airway management procedures if respiratory difficulties arise. In Canada, current commercially available treatments for acute attacks include C1-INH concentrates as well as the bradykinin receptor antagonist icatibant.[1,5]
- Short-term prophylaxis: This approach aims to reduce the risk of acute attacks and related morbidity and mortality during a time when there may be an increased risk of having such attacks and when avoidance of potential and known triggers is not possible. These situations would typically be associated with medical or dental interventions. Upper airway manipulation, including during dental surgery and intubation, is at particularly high risk due

to its association with upper airway swelling. C1-INH concentrates have been recommended as pre-procedure interventions in this context.[1,5]

- Long-term prophylaxis (LTP, or routine prevention): This approach involves initiating continuous regular treatment aimed at minimizing the number, frequency, and severity of attacks as well as reducing the burden of disease for patients when on-demand treatment does not sufficiently meet patient treatment requirements. It is important to note that no prophylactic regimen has been associated with the complete elimination of HAE attacks. As such, it is important that patients electing to use LTP also have access to on-demand therapy. C1-INH concentrates, as well as orally administered attenuated androgen therapy and antifibrinolytic drugs, may be used for LTP.[1,5] Lanadelumab was also recently introduced for LTP of C1-INH HAE in Canada.[7]

Pharmacotherapy of C1-INH HAE involves several interventions. While C1-INH replacement therapy with intravenous (IV) use of C1-INH concentrates is an important component, other pharmacotherapy modalities include SC use of bradykinin receptor antagonists (icatibant) and kallikrein inhibitors (e.g., ecallantide [Kalbitor], which is not currently licensed in Canada but can be accessed through Health Canada's Special Access Programme), IV use of recombinant human C1-INH (e.g., conestat alfa [Ruconest], which is also not currently licensed in Canada but can be accessed through Health Canada's Special Access Programme), as well as orally administered attenuated androgens (e.g., danazol) and antifibrinolytic drugs (e.g., tranexamic acid). C1-INH concentrate products or icatibant are typically used for on-demand therapy. Early treatment of C1-INH HAE attacks is recommended to reduce morbidity. For LTP of these attacks, regular administration of C1-INH concentrate is generally recommended; oral administration of danazol or tranexamic acid is also recommended for some patients.[1] Of note, although not formally approved for LTP of C1-INH HAE attacks, Berinert has been used for that purpose in clinical practice.[8] With the commercialization of lanadelumab in Canada in September 2018, SC use of monoclonal antibodies is also now part of the therapeutic armamentarium available for LTP of C1-INH HAE attacks.[7]

The purpose of this report is to inform policy decisions on C1-INH concentrate and non-plasma–derived products used in Canada for LTP of C1-INH HAE attacks, particularly if associated with C1-INH HAE 1 or C1-INH HAE 2. Accordingly, not all pharmaceutical interventions available for managing C1-INH HAE are included in the scope of this evaluation. More specifically, there are five products evaluated in this report. These, along with their approved use in Canada, are described in Table 2.

Table 2: C1-Esterase Inhibitor and Non-Plasma–Derived Products Available in Canada for Hereditary Angioedema Due to C1-Esterase Inhibitor Deficiency

Product Name (Brand Name)	Product Source	DIN and Concentration	Route of Administration	Manufacturer
Treatment of Acute HAE Attacks (On-Demand Therapy)				
C1-INH concentrate – human (Berinert)	Plasma-derived	02352575 (500 IU/vial) 02436078 (1,500 IU/vial)	IV	CSL Behring Canada Inc.[9-11]
Icatibant acetate (Firazyr)	Synthetic peptidomimetic	02425696 (30 mg/mL)	SC[a]	Shire Orphan Therapies LLC (Canadian distributor: Shire Pharma Canada ULC)[12,13]
Long-term Prophylaxis of C1-INH HAE Attacks				
C1-INH concentrate – human (Cinryze)	Plasma-derived	02395371 (500 IU/vial)	IV	ViroPharma Biologics Inc. (Canadian distributor: Innomar Strategies Inc.)[14,15]
C1-INH concentrate – human (Haegarda)	Plasma-derived	02468069 (2,000 IU/vial) 02468077 (3,000 IU/vial)	SC	CSL Behring Canada Inc.[b,16-18]
Lanadelumab (Takhzyro)	Human monoclonal antibody	02480948 (300 mg/2mL)	SC	Shire Pharma Canada ULC[19,20]

C1-INH = C1-esterase inhibitor; DIN = drug identification number; HAE = hereditary angioedema; IV = intravenous injection; SC = subcutaneous injection.

[a] Pre-filled syringe for slow subcutaneous injection.

[b] Product approved but not yet marketed in Canada.

Policy Issue

Utilization and reimbursement costs for C1-INH concentrate products for the treatment and prophylaxis of C1-INH HAE have increased significantly over recent years. In a 2017 brief, Canadian Blood Services (CBS) indicated that 30.5 million international units of C1-INH concentrate had been issued to hospitals served by CBS in 2016–2017; these amounted to a total cost of $54.4 million. Three years before, CBS had issued 12.8 million international units to Canadian hospitals.[21] Given the rise in the utilization of C1-INH concentrate and the associated costs, Canadian jurisdictions are interested in exploring opportunities to enhance the management of these products. Understanding how C1-INH concentrate products are currently being used and determining whether any changes to current CBS coverage policies are required to ensure the optimal use of these products is important. In the current context, it appears the main drivers of the increase in the utilization of C1-INH concentrate products are related to LTP of C1-HAE attacks. To that effect, it may be anticipated that the recent availability of products that can be administered subcutaneously, as opposed to intravenously, increases the pool of patients interested or eligible for such therapy. For example, some patients who may have elected in the past not to use C1-INH concentrate for LTP due to the IV route of administration may now be interested in using home-based routine prevention with one of the products available for SC administration. Another possible driver of the increased utilization of and spending on C1-INH concentrate products is the higher dose recommended for SC administration compared with the IV dose; i.e., the recommended SC dose may be up to three times (i.e., 40 IU/kg to 60 IU/kg) the approved IV dose of 20 IU/kg.[5] Based on these observations, the policy issue centres around determining how best to fund C1-INH concentrate and non-plasma–derived products so that

patients who will derive important benefits from using these products for LTP of C1-INH HAE attacks have access to these therapies, while ensuring such utilization represent an efficient use of health care resources. Two policy questions were developed to characterize this issue:

Policy Questions

1) What is the optimal use of available C1-INH concentrate and non-plasma–derived products for the LTP of C1-INH HAE attacks in Canada?
2) What are the implications of alternative policies for reimbursement of C1-INH concentrate and non-plasma–derived products for the LTP of C1-INH HAE attacks in Canada?

Methods

To address the two policy questions, this report includes four components. Each of these components aim to answer the following specific research questions:

Clinical Expert Consultation

1) How is LTP of C1-INH HAE attacks currently managed in Canadian clinical practice?
2) What are the characteristics of patients who are most likely to benefit from C1-INH concentrate and non-plasma–derived products for the LTP of C1-INH HAE attacks?
3) How might patients who are most likely to benefit from LTP of C1-INH HAE attacks be identified?

Utilization Analysis

1) What are the current utilization patterns of C1-INH concentrate products in Canada for the LTP of C1-INH HAE attacks?
2) What are the costs associated with this utilization?

Cost-Utility Analysis

1) What is the comparative cost-effectiveness of available C1-INH concentrate and non-plasma–derived products in Canada for LTP versus no LTP of C1-INH HAE attacks?

Budget Impact Analysis

1) What is the budget impact of providing prophylaxis for HAE patients in Canada?

A methodology was developed for each of the four report components in order to answer the related research questions.

Clinical Expert Consultation

A panel of four clinical experts from Ontario with expertise in the diagnosis and management of HAE in Canada was convened by CADTH for this consultation. The role of the expert panel was to elucidate: how LTP for the prevention of HAE attacks is currently used in Canadian clinical practice; the characteristics of patients most likely to benefit from LTP with C1-INH or lanadelumab to prevent HAE attacks; and how such patients are identified in Canadian clinical practice. Three of the four experts participated in a panel discussion during one teleconference, with a list of questions for discussion provided in advance of the teleconference. One expert provided written input using the same list of questions. A summary of the panel responses was prepared by CADTH staff after the consultation, which

was then validated by all panel members. The list of questions with detailed descriptions of the responses provided by the experts is presented in Appendix 1. Additional background documents summarizing information from clinical HAE guidelines as well as reimbursement recommendations and coverage policies relevant to LTP for the prevention of HAE attacks were also provided to the experts in advance of the teleconference (see Appendix 2 and Appendix 3).

Utilization Analysis

The objective of this analysis was to describe recent national utilization and spending trends by CBS on C1-INHs for LTP for the prevention of HAE attacks.

A drug-utilization analysis of C1-INHs nationally distributed between October 1, 2009 and March 31, 2019 was conducted. Two C1-INHs used as LTP for the prevention of HAE attacks were available in Canada at the time of this report and were included in this analysis: Berinert and Cinryze. Cinryze is approved by Health Canada for routine prevention of angioedema attacks in adults and adolescents. Berinert is approved by Health Canada for the treatment of acute abdominal, facial, and laryngeal attacks of HAE of moderate to severe intensity in pediatric and adult patients. However, Berinert is often used beyond the Health Canada indication as an LTP treatment for the prevention of HAE attacks. When used in this manner, Berinert may be administered via IV or SC routes.

To conduct this analysis, data supplied by CBS on product distribution were used. These data reported the total number of units distributed to blood banks by calendar quarter and their associated cost per quarter. The data were reported by product and by jurisdiction (province or territory). The total units of C1-INH distributed by CBS quarterly, the total cost of the drugs distributed, and the rates of use by jurisdiction (province or territory) were reported. All measures were reported as units. A comparison of provincial usage was reported as rates per 1,000 population. Population data for 2018 were obtained from Statistics Canada's provincial Vital Statistics.[22] This analysis does not include data from Quebec, as blood products are distributed in that province through Héma-Québec.

A cross-sectional analysis of C1-INH concentrate utilization and spending was conducted by identifying the quarterly number of units distributed by CBS and the associated cost over the study period. Interventional time series autoregressive integrated moving average (ARIMA) models were fit to the data, as were Holt–Winters method models with linear smoothing. Both models are commonly used in time-series forecasting, as they allow adjustments for current trends and seasonality. Importantly, both methods place less weighting on distant data points, allowing the model to adjust to shifting trends to calculate projections. The best-fitting model was selected to forecast the total utilization and spending up to the first quarter of 2021 based on trends observed in the 10 years prior. Of note, as available data were not linked to the reason for use, it was not possible to attribute their utilization to the actual indication for their use, i.e., treatment of acute HAE attacks or the LTP of these attacks.

Lastly, user-level data were received from the British Columbia Provincial Health Services Authority. This data contained information on the number of individuals receiving C1-INH concentrate, the number of new users, and the total number of units dispensed per quarter. This information was limited to only those drugs distributed by CBS's British Columbia blood bank to British Columbia and Yukon residents. The data were available from Q1 2009 to Q2 2019. Using this data, the number of new and ongoing users per quarter and the average number of units per user per quarter were reported.

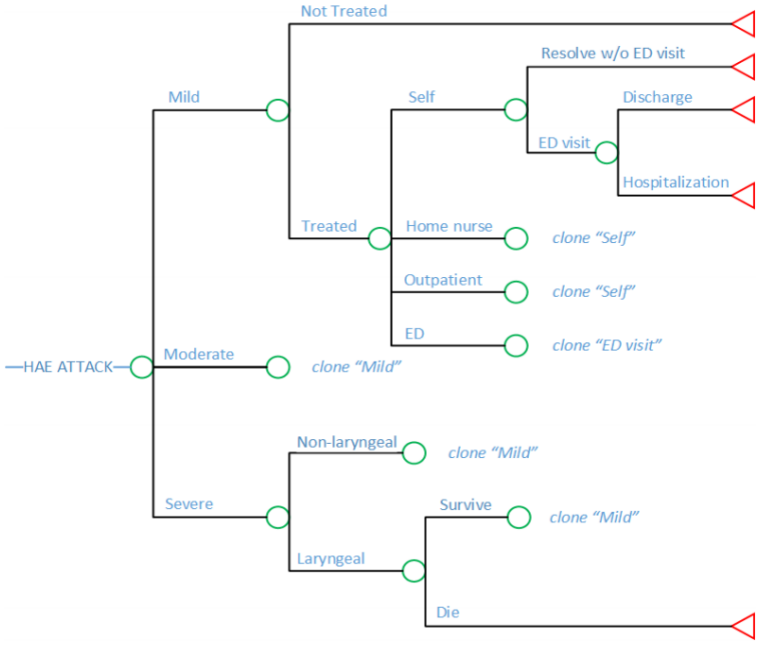
Economic Evaluation

The objective of this analysis was to explore the comparative cost-effectiveness of available C1-INH concentrate and non-plasma–derived products in Canada for LTP versus on-demand treatment alone for C1-INH HAE attacks.

CADTH conducted a scoping review in August 29, 2019 to identify any published economic evaluations on the LTP of HAE. CADTH identified eight economic evaluations, six of which were not relevant to our research question. CADTH identified the most relevant evaluation, which was a study conducted by the Institute for Clinical and Economic Review (ICER) in the US on the effectiveness and value of LTP treatment with lanadelumab and C1-INH concentrate for HAE attacks. In order to leverage the research already conducted, CADTH contacted ICER and the developers of the ICER model (researchers at the University of Washington[23]) to obtain a copy of the model used in the analysis. After obtaining the model, CADTH conducted an internal technical review of the model to assess the feasibility of adapting the economic model to the health care system in Canada. During the internal review, CADTH concluded that adapting the ICER economic model was possible and the model would address the research question. The developers of the model were consulted as needed to ensure a proper understanding of the model structure and the inputs and assumptions used in the model.

CADTH adapted the ICER model to assess the lifetime costs, health outcomes, and cost-effectiveness of LTP for HAE attacks compared with no LTP.[2,23] A complete description of the model can be found in the ICER report.[2] Briefly, ICER developed a Markov model based on the following two health states: alive with HAE, and dead. All patients in the model started in the alive state and could experience attack events or death during a model cycle (the risk of these events depended on the treatment being received). Severity of attack and anatomical location of severe attacks (i.e., both laryngeal and non-laryngeal) were tracked in the model. Figure 1 describes the HAE attack pathway, which reflects how costs and utilities were weighted.

Figure 1: Hereditary Angioedema Attack Pathway



ED = emergency department; HAE = hereditary angioedema.
Source: ICER report.[2]

The perspective of the ICER model was that of the US health care system; however, the economic model was adapted by CADTH to reflect a Canadian context (Appendix 4). Changes made to the model were related to changes in input parameters and are listed in Table 26. Briefly, the following changes were made:

- Only therapies approved in Canada were included in the analysis (conestat alfa and ecallantide were excluded from the analysis as they are not approved in Canada, and Haegarda was included only as an exploratory analysis, as it is approved but not currently marketed in Canada).
- The discount rate was set to 1.5% as per Canadian guidelines.[3]
- Canadian administration, monitoring, and drug costs were used in the model.

Face validity of the model was achieved through consultation with Canadian clinical experts throughout the research phase to ensure the model was consistent with current clinical knowledge and Canadian practice. The clinical pathway was validated with Canadian clinical experts; clinical inputs were validated by clinical experts and by CADTH clinical reviewers. The revised model was sent to the University of Washington for a technical review to ensure the modifications made for the purpose of this project were implemented correctly.

The adapted Markov model was used to compare the total costs and quality-adjusted life-years (QALYs) of the three drugs used for LTP of HAE attacks in Canada (lanadelumab, Cinryze, and Berinert) with no LTP. On-demand treatment for acute attacks consisted of treatment with the following drugs approved in Canada: Berinert and icatibant. The analysis was conducted from the Canadian public payer perspective over a lifetime horizon. The model cycle length was one month. Both the outcomes and costs accrued beyond the first

year of the model were discounted at a rate of 1.5%, per CADTH guidelines. The target population reflected the weighted average of the baseline characteristics across the three pivotal clinical trials of the LTP therapies.[24-26] LTP was assumed to reduce the number of HAE attacks compared with no LTP, and treatment effect on the number of attacks was based on the key clinical trials.[24-26] Use of Haegarda was assumed to alter the distribution of attack severity, according to data from the COMPACT study.[25] All clinical data were validated by CADTH clinical reviewers. EuroQol 5-Dimensions questionnaire (EQ-5D) scores from a Swedish study of HAE patients experiencing acute attacks[27] were used to estimate the attack disutility associated with mild, moderate, and severe attacks. The model tracked number of attacks (including attack severity and anatomical location of severe attacks), patient survival, time spent "attack-free," QALYs, and health care costs in each cycle. Differences in QALYs and costs between each LTP therapy and no LTP were used to calculate the incremental cost-effectiveness ratios. Details on model parameter values can be found in Appendix 4.

Some of the key model assumptions are the following:

- LTP therapies were assumed to be taken on a lifelong basis.
- All patients on LTP were assumed to have access to on-demand treatment for acute attacks.
- Mild and moderate attacks last one day, severe attacks last two days, and untreated attacks last an extra day.
- Death can occur in case of laryngeal involvement.

A full list of key assumptions can be found in Appendix 4.

The base case reflects the probabilistic results based on 5,000 simulations. In the base case, pairwise Incremental cost-utility ratios (ICURs) were calculated for each LTP therapy versus no LTP, as well as sequential ICURs, including all LTP therapies.

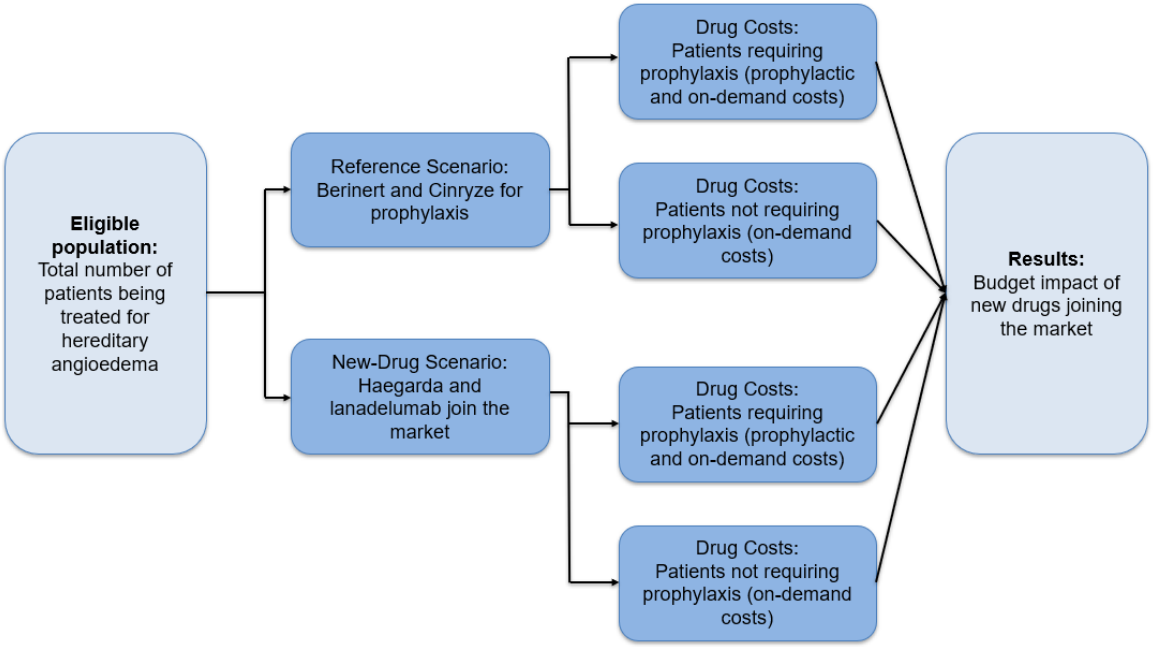
The following scenario analyses were explored by CADTH:

- Haegarda was included as a comparator using the following two costing scenarios:
  - costs provided by CBS
  - costs are the same as for Cinryze.
- Alternative assumptions for baseline attack rates were explored:
  - the impact of alternative baseline attack rates (one to 10 attacks per month) was examined
  - the assumption that mild, moderate, and severe attacks take the same amount of time to resolve (e.g., 48 hours if treated and 72 hours if untreated, as per Canadian clinical expert feedback).
- Threshold analyses were performed by altering the price of the interventions to estimate the maximum prices that would correspond to WTP thresholds of $50,000, $100,000, $150,000, $200,000, $300,000, and $500,000 per QALY.
- Alternative dosing for lanadelumab was explored as per the product monograph, which states that "a dosing interval of 300 mg every four weeks is also effective and may be considered if the patient is well controlled (e.g., attack-free) for more than six months."[20]
- A societal perspective, including indirect costs, was explored.

Budget Impact Analysis

The objective of the budget impact analysis (BIA) was to estimate the financial impact of new therapies for C1-INH HAE becoming accessible to patients and the financial impact of providing LTP therapies. The BIA intends to address the budget impact of new drugs for LTP of HAE attacks becoming accessible, in comparison with currently used LTP therapies. In addition, the BIA attempts to estimate the budget impact of providing LTP to HAE patients in comparison with providing only on-demand therapies. The BIA was built in Microsoft Excel using a prevalence-based approach. A static analytic framework was adopted in the model to compare two scenarios: a reference scenario, where LTP with Berinert and Cinryze is available; and a new-drug scenario, where Haegarda and lanadelumab are available. The annual cost of LTP in each scenario was multiplied by the number of patients requiring LTP. The annual cost of on-demand therapy is dependent on the LTP treatment being received (Table 10), as the number of annual attacks varies by treatment (Table 35 in Appendix 5). When estimating annual costs, no reduction in attack frequency was made for patients not requiring or receiving LTP. In each scenario, costs for the current year were calculated by summing the costs associated with LTP and on-demand therapy in patients requiring LTP, plus the costs of on-demand therapy in patients not requiring LTP. To calculate the budget impact of new drugs becoming accessible to patients, the total costs for patients requiring LTP and those not requiring LTP were summed for both the reference and the new-drug scenarios, and the total costs of the new-drug scenario were subtracted from the reference scenario (Figure 2).

Figure 2: Schematic of Budget Impact Analysis Modelling Approach for New-Drug Scenario



In addition to this analysis, an exploratory analysis was conducted to compare two scenarios: a reference no-LTP scenario, where it is assumed that no patients will receive LTP; and a prophylaxis scenario, where patients who require prophylaxis receive treatment

with currently available C1-INH concentrate products (Berinert or Cinryze). These two scenarios were compared together. To calculate the budget impact of providing LTP compared with not providing LTP, the total costs of the no-LTP scenario were subtracted from the LTP scenario.

Patient Population

Exact prevalence for HAE in Canada is unknown. An estimated prevalence of 1 in 50,000 is often cited in the literature;[1] however, this is a rough estimate originally reported in a 1996 paper on HAE and might therefore be outdated.[28,29] A recent systematic investigation of the population-based prevalence of HAE revealed prevalence estimates ranging from 1:64,000 to 1:93,000, indicating that HAE may be less prevalent than initial estimates.[6]

A prevalence-based approach to the BIA was taken using a three-year analysis time frame. In the base case, a prevalence of 1:67,000 was assumed.[6] This prevalence estimate comes from an epidemiological investigation of HAE prevalence in Denmark and is the most up-to-date estimate available. Furthermore, in a recent review of HAE epidemiological studies, this estimate was considered to represent the best estimate of HAE prevalence.[6] As the exact number of HAE patients is unknown, alternative prevalence estimates were examined in the scenario analyses.

Estimates relating to the total population of Canada and provincial jurisdictions were sourced from Statistics Canada population estimates for the year 2019 (Quebec was excluded from the analysis).[22] It was assumed that 100% of this population would be covered by CBS. As jurisdiction-specific prevalence estimates are not available, the base case was conducted from the perspective of the total Canadian population. However, CADTH has provided the results by province, based on the assumption of equal prevalence across jurisdictions (Appendix 5).

There are no estimates on the number of HAE patients who are diagnosed in Canada. In clinical practice, some patients with HAE may not be accurately diagnosed, as a proportion of patients may be misdiagnosed as having acquired angioedema, angiotensin-converting enzyme inhibitor–induced angioedema, mast cell–mediated angioedema, and idiopathic angioedema.[30] As the percentage of patients diagnosed is associated with high levels of uncertainty, CADTH calibrated the BIA by selecting the diagnosis rate that best reproduced CBS annual spending on C1-INH concentrate products. Based on this calibration exercise, CADTH assumed that 65% of HAE patients will be diagnosed. This assumption was further validated by CBS and by the clinical expert consulted by CADTH for the economic evaluations. Given uncertainty regarding the number of incident cases, changes in diagnostic patterns, and mortality in this population, a static modelling approach was used; that is, it was assumed there would be no population growth, no new cases entering the population, and no changes in the percentage of patients diagnosed over the three-year time horizon.

Real-world treatment patterns of HAE patients in Canada suggest that 92.2% of the patients diagnosed with HAE receive on-demand treatment for HAE attacks, whereas 64.7% of the patients diagnosed with HAE receive LTP. Of those patients receiving LTP, 63.6% receive C1-INH.[31] Therefore, the proportion of patients requiring LTP with C1-INH or lanadelumab was estimated to be 41%. As the number of patients currently using LTP is unknown, and clinical experts indicated that a greater percentage of patients may require LTP, alternative percentages of patients on prophylaxis were tested in scenario analyses. All population-based inputs are provided in Table 3.

Table 3: Population Inputs

Parameter	Estimate	Source
Population size	29,104,297	Statistics Canada 2019 population estimates. Total population of Canada minus the population of Quebec[22]
Percentage of population covered by CBS	100%	Assumption
Prevalence of HAE	0.0015%	Aygoren-Pursun et al., 2018[6]
Percentage of HAE patients diagnosed	65%	Assumption
Percentage of HAE patients using any treatment	92.2%	Mendivil et al., 2019[31]
Subgroup 1: Percentage of HAE patients requiring LTP with C1-INH or lanadelumab	41%	Calculation from figures reported in Mendivil et al., 2019[31] (64.7% of HAE patients receiving LTP × 63.6% patients using C1-INH)
Subgroup 2: Percentage of HAE patients not requiring LTP	59%	Calculation: 100% to 41%

C1-INH = C1-esterase inhibitor; CBS = Canadian Blood Services; HAE = hereditary angioedema; LTP = long-term prophylaxis.

Using the preceding population inputs, it was estimated that there are 434 HAE patients in Canada (excluding Quebec), and only 282 of these patients have been diagnosed. Of the patients diagnosed, 260 are estimated to be receiving an on-demand treatment for HAE. And, of those receiving treatment, 107 patients require LTP. All patient numbers used in the BIA are provided in Table 4.

Table 4: Population Estimates for Budget Impact Analysis

Parameter	Estimate	Source
Number of HAE patients	434	Total population × HAE prevalence
Number of patients diagnosed	282	Number of HAE patients × % diagnosed
Number of patients receiving treatment	260	Number of patients diagnosed × % receiving treatment
Number of patients requiring LTP	107	Number of patients receiving treatment × % requiring LTP
Number of patients not requiring LTP	153	Number of patients receiving treatment × % not requiring LTP

HAE = hereditary angioedema; LTP = long-term prophylaxis.

Time Horizon

The model examined the budget impact of prophylaxis with C1-INH concentrate products in the current year (2019) and over a three-year time horizon (2020 to 2022).

Perspective

The perspective of this analysis is the Canadian publicly funded payer for C1-INH concentrate and non-plasma–derived products. Only drug costs were considered in the analysis. While the perspective taken in the base case was that of Canadian jurisdictions covered by CBS (total Canadian population minus the population of Quebec), the model allows for the viewing of the budget impact results for each of the following jurisdictions:

- British Columbia
- Alberta
- Saskatchewan
- Manitoba
- Ontario
- New Brunswick

- Nova Scotia
- Prince Edward Island
- Newfoundland and Labrador
- Yukon, Nunavut, and Northwest Territories

Intervention Scenarios and/or Strategies

To examine the budget impact of currently available LTP therapies, as well as the impact of introducing LTP therapies that are not currently available in Canada, the BIA compares two scenarios:

1. Reference scenario: Currently available LTP therapies (off-label Berinert and Cinryze).
2. New-drug scenario: Haegarda and lanadelumab become available.

The LTP doses used in the BIA are provided in Table 5. Despite Berinert being indicated only to treat acute attacks, it is also being used for LTP, according to clinical expert feedback. Patients using Berinert for LTP may administer it intravenously or subcutaneously. Based on clinical expert feedback, it was assumed that of all patients using Berinert for LTP, 75% of patients use it subcutaneously, while the remaining 25% use it intravenously. The proportion of patients using Berinert subcutaneously for LTP is explored in the scenario analyses. Different Berinert LTP doses are used, depending on the route of administration (Table 5).

Table 5: Interventions and Dosages for Hereditary Angioedema Prophylaxis

Therapy	Route of Administration	Dose	Dosage Form
Berinert	IV	20 IU/kg twice weekly[a]	Vial: 500 IU, 1,500 IU
Berinert	SC	60 IU/kg twice weekly[a]	Vial: 500 IU, 1,500 IU
Cinryze	IV	1,000 IU twice weekly	Vial: 500 IU
Haegarda	SC	60 IU/kg twice weekly	Vial: 2,000 IU, 3,000 IU
Lanadelumab	SC	300 mg every two weeks	Solution for SC injection: 300 mg/2mL

IV = intravenous; SC = subcutaneous.

Note: All doses and dosage forms provided from respective product monographs, unless specified.

[a] Routine prophylactic dose according to clinical expert input.

While the current distribution of treatments used for LTP is unknown, more patients are using Berinert than Cinryze, according to feedback from clinical experts and CBS. In addition, to account for the impact of unmet need on the budget, we have assumed that some patients who require LTP are not receiving LTP. While the exact unmet need is unknown, based on clinical expert opinion, this was estimated to represent [redacted] of patients who require LTP. Under these assumptions, the market shares of treatment options for the reference scenario are provided in Table 6. Market shares were calculated based on the number of patients estimated to be using Cinryze, according to CBS feedback. It was therefore expected that [redacted] of patients in Canada are using Cinryze, [redacted] of patients requiring LTP are not receiving LTP, and the remaining [redacted] of patients are using Berinert for LTP. For the reference scenario, it is assumed that the treatment mix for LTP therapies will not change from current use over the three-year time horizon if no new drugs become available.

Table 6: Reference Scenario: Current Hereditary Angioedema Long-Term Prophylaxis Therapies Only

Comparator	Current Year (%)	Year 1 (%)	Year 2 (%)	Year 3 (%)
Berinert	[redacted]	[redacted]	[redacted]	[redacted]
Cinryze	[redacted]	[redacted]	[redacted]	[redacted]
No LTP	[redacted]	[redacted]	[redacted]	[redacted]

LTP = long-term prophylaxis.

In the new-drug scenario, the treatment mix for the current year assumes that no patients are currently using Haegarda or lanadelumab. Should Haegarda and lanadelumab become widely available, the potential update of these therapies is uncertain. Given the paucity of data sources for estimating the uptake of a new drug, the predicted uptake of Haegarda and lanadelumab over the modelled time horizon was estimated from clinical expert opinion and was assumed to be [redacted], [redacted], and [redacted] for Haegarda in year 1, year 2, and year 3, respectively. For lanadelumab, the predicted market uptake in years 1, 2, and 3 was estimated to be [redacted], [redacted], and [redacted], respectively. Based on the predicted uptake of the new therapies, the market shares of current therapies and no prophylaxis were reduced proportionately (Table 7).

Table 7: New-Drug Scenario: Haegarda and Lanadelumab Become Accessible to Patients

Comparator	Current Year (%)	Year 1 (%)	Year 2 (%)	Year 3 (%)
Berinert	[redacted]	[redacted]	[redacted]	[redacted]
Cinryze	[redacted]	[redacted]	[redacted]	[redacted]
Haegarda	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab	[redacted]	[redacted]	[redacted]	[redacted]
No LTP	[redacted]	[redacted]	[redacted]	[redacted]

LTP = long-term prophylaxis.

All patients are assumed to have access to on-demand therapies for acute attacks. According to clinical experts, the type of on-demand therapy patients will use will depend on their current LTP treatment, as clinicians may encourage patients to use a dose of their LTP treatment to treat acute attacks. Table 8 provides the on-demand therapies used by patients, according to their LTP treatment. It was assumed that most patients ([redacted]) receiving either Berinert or Cinryze for LTP would use the same treatment to treat acute attacks, with the remaining patients ([redacted]) using icatibant. Patients using Haegarda and no LTP were assumed to use the same on-demand therapies as Berinert LTP patients. It was assumed, based on expert feedback, that lanadelumab patients would prefer an SC route of administration for their on-demand treatments and, therefore, most patients on lanadelumab ([redacted]) will use icatibant as on-demand therapy. While Cinryze may be used to treat acute attacks, it was assumed there would be no such use of Haegarda or lanadelumab, as it is unknown how these products will be used by patients, given they are either not yet commercially available or newly commercialized in Canada. Finally, it was assumed that patients will use only one type of on-demand therapy to treat acute attacks, and that the on-demand treatment mix would not change in the coming years.

Table 8: On-Demand Treatments by Long-Term Prophylaxis Treatments

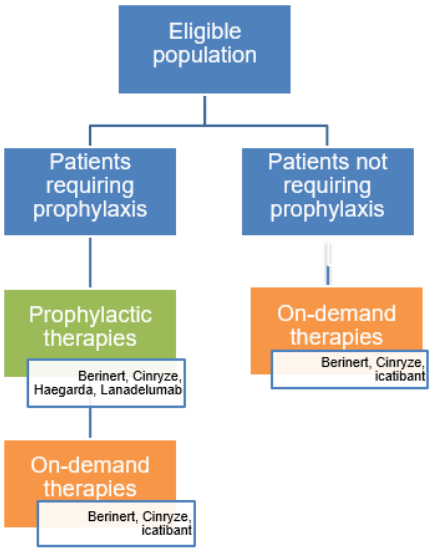
		LTP Treatments (%)				
		Berinert	Cinryze	Haegarda	Lanadelumab	No LTP
On-Demand Treatments	Berinert	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Cinryze	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Icatibant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LTP = long-term prophylaxis.

Analytic Framework Description

Based on the assumptions and subgroups outlined, Figure 3 presents the structure of the BIA. This figure demonstrates that the entire population of HAE patients is divided into those requiring and not requiring prophylaxis. Depending on the scenario, patients requiring LTP will receive treatment with either Berinert, Cinryze, Haegarda, or lanadelumab. Patients requiring LTP will also receive on-demand treatments. Patients not requiring LTP will only receive on-demand treatment with Berinert, Cinryze, or icatibant.

Figure 3: Structure of Budget Impact Analysis



Clinical Inputs

In the BIA, all patients experience acute attacks and have access to on-demand therapy. The baseline monthly attack frequency for patients requiring LTP was assumed to be equal to the weighted average across the pivotal clinical trials for the interventions (3.39) (Table 9).[24-26] It was assumed that patients who do not require LTP will have 1.34 attacks a month, based on a study investigating real-world treatment patterns of HAE patients in Canada.[31]

Patients receiving prophylaxis have a reduction in their attack frequency associated with their respective LTP therapies. The percentage reduction in attack frequency was sourced from the pivotal trials for each LTP therapy (Table 9).[24-26] It was assumed that Berinert patients would have the same mean reduction in attack frequency as Haegarda. Due to a paucity of clinical data regarding the effect of LTP on attack severity, only attack frequency was considered in the BIA.

Table 9: Clinical Inputs

Parameter	Value	Source
Monthly Baseline Attack Frequency		
Patients requiring LTP	3.39	Weighted average of baseline values across pivotal trials[24-26]
Patients not requiring LTP	1.34[a]	Mendivil et al., 2018[31]
Percentage Mean Reduction in Attack Frequency		
Berinert	84.0%	Assumed to be equal to Haegarda
Cinryze	50.5%	Zuraw, 2010[26]
Haegarda	84.0%	Longhurst, 2017[25]
Lanadelumab	86.9%	Banerji, 2017[24]

LTP = long-term prophylaxis.

[a] Assumes that patients not using prophylaxis from 2014 onward would make up this group. The calculation assumes that patients will have 16.1 attacks annually (1.34 attacks monthly).[31]

Cost Inputs

Data Sources

The costs of Berinert, Cinryze, and Haegarda were provided in US dollars by CBS as confidential costs. These costs were converted to Canadian dollars using historical Bank of Canada exchange rates (average rate from January 1, 2018 to December 31, 2018).[32] Lanadelumab costs were estimated based on a back calculation from a British Columbia Pharmacare report on lanadelumab.[33] Icatibant costs were sourced from the IQVIA database.[34]

Per-dose LTP therapy costs were calculated based on doses specified in each treatment's product monograph and on clinical expert input (Table 5).[15,18,20] Weight-based doses were calculated based on the weighted average of the male and female weights used in the economic evaluation (Table 23). Annual costs of therapy were calculated according to each treatment's dosing interval. For Berinert, Cinryze, and Haegarda, a twice-weekly dosing schedule was used, resulting in 104 doses per year.[15,18] For lanadelumab, a schedule of one dose every two weeks was used, resulting in 26 doses per year.[20] Annual LTP Berinert costs assumed that 75% of patients will be using an SC route of administration and 25% will administer intravenously. All costs were calculated to include drug wastage (Table 10).

Table 10: Annual Costs for Long-Term Prophylaxis

Treatment	Annual LTP Cost ($)	Cost per On-Demand Dose ($)
Berinert	[redacted][a]	[redacted]
Cinryze	[redacted]	[redacted][b]
Haegarda	[redacted]	NA
Lanadelumab	533,988[c]	NA
Icatibant	NA	2,700[d]

LTP = long-term prophylaxis; NA = not applicable.

Note: All costs provided by Canadian Blood Services unless otherwise specified. Weight-based doses were calculated using a weight of 80.32 kg. All doses and dosage forms are from respective product monographs, unless specified.

[a] Cost calculated by taking the annual costs of Berinert prophylaxis by subcutaneous and intravenous route and weighting each by the proportion of patients using subcutaneous ([redacted]) and intravenous ([redacted]) administration.

[b] Cinryze on-demand dose assumed to be 1,000 IU/kg.

[c] Source: British Columbia Pharmacare Report.[33]

[d] Source: IQVIA database.[34]

The on-demand doses for Berinert and icatibant were sourced from product monographs.[9,13] The dose for use of Cinryze on-demand was assumed to be 1,000 IU, based on clinical expert input. The annual cost of each on-demand treatment was calculated by multiplying the number of monthly attacks associated with each treatment by 12 months to estimate the number of attacks per year (Table 35 in Appendix 5). This value was then multiplied by the cost of one on-demand dose to determine the costs of on-demand doses for patients requiring LTP.

Analyses

Base Case

The following table summarizes the key assumptions made in the base-case analysis of this BIA.

Table 11: Base-Case Assumptions

Parameter	Assumption	Additional Comment(s)
Prevalence	1:67,000[6]	The prevalence of HAE in Canada is unknown.
Diagnosis rate	65%	The current number of HAE patients in Canada is unknown. In order for BIA spending in the current year to approximate CBS annual spending, a diagnosis rate of 65% was assumed.
Population growth and number of new patients	It was assumed that the total number of patients remained constant over time and that no new patients (incident population) entered the BIA from year 1 to year 3.	As there is no incidence data for HAE, it was assumed the number of patients dying from HAE would be approximately equal to the number of new HAE patients being diagnosed.
Off-label use of therapies on demand	There is no off-label use of Haegarda or lanadelumab as on-demand therapies.	As these therapies are not currently available in Canada, it is unknown how they will be used by clinicians and patients.
On-demand therapies	Patients will only use one on-demand therapy to treat acute attacks.	Feedback from the clinical expert has indicated that patients receiving LTP may use that medication as well as icatibant to treat acute attacks. However, due to an absence of data on the market shares of on-demand treatments and to simplify the BIA, it was assumed that patients use just one type of therapy to treat acute attacks.

Parameter	Assumption	Additional Comment(s)
Treatment mix: current LTP therapies	The current LTP treatment mix does not change over time if new drugs do not become accessible to patients.	This assumption was deemed to be appropriate by clinical experts.
Treatment mix: on-demand therapies	The on-demand therapy treatment mix does not change over time.	This assumption was deemed to be appropriate by clinical experts.
Severity of attacks	LTP treatment influences only the frequency, not the severity, of HAE attacks.	CADTH was unable to incorporate this into the model due to data paucity, as only the Haegarda trial assessed the influence of LTP on attack severity.

BIA = budget impact analysis; CBS = Canadian Blood Services; HAE = hereditary angioedema; LTP = long-term prophylaxis.

Some base-case assumptions were tested using a range of different scenarios. The scenarios explored and inputs used for the sensitivity analyses are presented in Table 36.

Scenario Analyses

Scenario analyses were conducted to test the effect of assumptions and inputs on the BIA results. Scenarios are conducted on inputs used to estimate the number of HAE patients (prevalence of HAE, percentage of HAE patients diagnosed, and percentage of HAE patients requiring LTP). Alternative patient weights, Berinert LTP dosing, and baseline attack frequency estimates were explored in sensitivity analyses.

Results

Clinical Expert Consultation

The following information is a summary of the responses obtained from the clinical expert consultation conducted by CADTH in October 2019.

Current Treatment Paradigm for Long-Term Prophylaxis for Prevention of Hereditary Angioedema Attacks Due to C1-Esterase Inhibitor Deficiency

Treatment Goals and Therapies Used for Long-Term Prophylaxis

According to the panellists, the goal of LTP for prevention of C1-INH HAE attacks is to allow patients to live a normal life: to work, go to school, perform daily activities, and to participate in recreational and social activities. Without LTP, patients may avoid certain activities that can trigger their attacks, such as strenuous exercise or working a night shift.

LTP is considered for patients who need to control frequent and/or severe C1-INH HAE attacks. In addition, the impact of these attacks on patients in terms of health-related quality of life and ability to perform their usual activities must be taken into consideration when evaluating a patient's suitability for LTP.

The panellists estimated that 50% to 70% of patients in Canada with C1-INH HAE are currently receiving LTP for the prevention of attacks. A retrospective study in 51 patients with HAE at four Canadian centres found that 65% of patients were receiving LTP.[31] Most patients on LTP are receiving C1-INH concentrate administered either intravenously or subcutaneously, while the remainder receive oral LTP with either androgens (e.g., danazol) or antifibrinolytics (e.g., tranexamic acid). At the time the expert consultation was conducted, lanadelumab was available through exceptional access only. While the panellists expected the use of oral LTP in Canada to decline over time, they recognized that some patients already receiving oral LTP may prefer to stay on their current regimen rather than switch to LTP with a C1-INH concentrate.

In addition to LTP, all patients with C1-INH HAE usually also have an on-demand treatment available for breakthrough attacks.

Choice of Therapy for Long-Term Prophylaxis

The panellists indicated that in current Canadian clinical practice, most patients with C1-INH HAE are initiated on C1-INH concentrate or icatibant for on-demand treatment of acute attacks. If patients have more frequent attacks, they may gradually transition to using C1-INH concentrate twice weekly, which is the dosage regimen for LTP. Patients may also transition from LTP with oral danazol to LTP with IV or SC C1-INH concentrate if danazol is not effective at a dose of up to 200 mg, or if patients experience many adverse effects with danazol.

In patients receiving oral LTP, the use of danazol is more common than the use of tranexamic acid. Tranexamic acid is associated with gastrointestinal adverse effects and evidence for its efficacy is lacking. Long-term use of danazol is associated with adverse effects, including masculinizing effects and risk of hepatocellular carcinoma and, according to the panellists, is therefore not suitable for patients unless they prefer it and agree to long-term monitoring. The masculinizing adverse effects may be particularly troublesome for female patients.

Pediatric patients and patients with C1-INH HAE who are pregnant cannot receive oral LTP with danazol; instead, these patients receive C1-INH concentrate therapy. Patients on danazol who are planning for pregnancy or who become pregnant discontinue danazol. The panellists also noted that patients with C1-INH HAE who are pregnant would not receive lanadelumab, as there is little experience with its use during pregnancy.

The route of administration also plays a role in the choice of therapy for LTP. Injectable routes of administration may deter some patients from initiating treatment with currently available C1-INH concentrate therapies or lanadelumab. According to the panellists, some patients may rely on on-demand treatment with icatibant or choose not to treat their attacks rather than use LTP with C1-INH concentrate due to the need to inject these drugs. Use of an implanted device to facilitate IV injection, such as a port-a-cath, is generally not used to facilitate IV access, as it can lead to thrombosis and infection. However, based on the panellists' clinical experience, patients who are willing to be trained in performing self-administered IV injection can do so successfully. Patients who are significantly impacted by their attacks are usually motivated to use self-administered IV therapy. According to the panellists, administration using the SC route of administration, either twice a week with C1-INH concentrate or every two weeks with lanadelumab, is more feasible for patients than IV administration twice a week. The panellists mentioned the possibility that some clinicians currently treating patients with HAE may not be aware of or may not be comfortable with using SC C1-INH concentrate beyond the Health Canada–approved indication, and their patients may therefore not initiate LTP with C1-INH concentrate despite frequent attacks.

Coverage of therapies and ease of access (e.g., a patient may live far away from a blood bank) can also have an impact on which therapies patients receive.

At the time of the expert consultation, Haegarda was not available in Canada, although it is approved by Health Canada as an LTP treatment for the prevention of C1-INH HAE attacks. The panellists expected that if Haegarda or lanadelumab became more accessible in Canada, the proportion of patients with HAE who receive LTP would likely increase, though they had difficulty predicting the amount of increase. The availability of Haegarda (a C1-INH concentrate approved for SC administration) would likely increase the use of this form of LTP. If lanadelumab were more accessible, its use would also likely increase and the

proportion of patients using C1-INH concentrate for LTP would be expected to decrease, as patients may prefer the recommended dosing for lanadelumab over the dosing schedules associated with C1-INH concentrate for LTP (i.e., every two weeks compared with every three to four days, respectively).

Optimal Use of C1-Esterase Inhibitor and Lanadelumab for Long-Term Prophylaxis

Suitable Patient Population

The panellists agreed that patients who are likely to benefit from LTP with C1-INH concentrate or lanadelumab are those with frequent and/or severe C1-INH HAE attacks whose quality of life and social functioning are adversely impacted by their condition. Patients who require frequent hospitalization or emergency visits to control their C1-INH HAE attacks should also be considered for LTP. Patients who may benefit from SC LTP specifically with C1-INH concentrate or lanadelumab include those whose C1-INH HAE attacks cannot be treated with icatibant (due to lack of access or lack of response to treatment) and who are unable to self-administer on-demand IV C1-INH concentrate treatment. The panellists estimated that at least 50% of patients with C1-INH HAE would benefit from LTP and noted that some patients not currently on LTP would likely benefit from using this form of prophylaxis.

The panellists noted it is difficult to predict the degree of benefit individual patients might experience after initiating LTP, as the relationship between patients' baseline attack characteristics (i.e., frequency and severity) and therapeutic response is not known. For example, patients with very different baseline attack frequencies may end up with similar attack frequencies after initiating LTP. Effectively, these patients would have different relative reductions in attack frequency and clinicians are unable to predict this response. It is also unclear if some patients may experience more benefit from one type of treatment (C1-INH concentrate or lanadelumab) over another.

While clinical trial results for LTP with SC C1-INH concentrate have shown it is efficacious in reducing attacks, it is harder to predict who might benefit in the real world versus in a clinical trial. For example, adherence to the recommended dosage in the real world may be different from the clinical trial setting.

Identifying Suitable Patients

The decision to initiate LTP with C1-INH concentrate or lanadelumab is based on several factors. The following factors identified from the treatment-initiation criteria gathered from international jurisdictions (see Appendix 3 for more details) were discussed by the panel.

Age

Age is considered in the context of the approved indications for C1-INH concentrate products and lanadelumab. However, clinicians may use these treatments beyond the ages specified on the label if there are no other options or if clinical guidelines recommend use beyond approved indications.

Diagnosis

A confirmed diagnosis of C1-INH HAE 1 or C1-INH HAE 2 is important for initiating LTP with the currently available drugs, and the diagnosis of C1-INH HAE 1 and C1-INH HAE 2 is standardized across Canada. Diagnosis should be based on the presence of a low C1-INH functional level and/or low C1-INH antigenic level. A low C4 level should not be required, as C4 level may be normal in patients with C1-INH HAE 1 or C1-INH HAE 2. The panellists

acknowledged that C1-INH concentrate LTP may benefit patients with HAE-nC1INH, though there is currently insufficient evidence to support any recommendations for such use.

Frequency and Severity of Attacks

There was agreement among the panellists that there should be no cut-off in terms of achieving pre-specified levels of frequency or severity of C1-INH HAE attacks for determining whether a patient should receive LTP with C1-INH concentrate or lanadelumab. Both frequency and severity of C1-INH HAE attacks need to be considered, in addition to the impact of the condition on patients' health-related quality of life and their ability to live a normal life. For example, an attack frequency as low as one per month has significant impact if the attack requires hospitalization (as is the case for laryngeal attacks) and keeps the patient away from work for several days. These factors need to be considered along with patient safety, and it would be very difficult to impose limits on use that could apply to all patients.

The panellists agreed that assessment of C1-INH HAE attack severity can be difficult, as early on-demand treatment of an attack can prevent or greatly mitigate symptoms, and it would be inappropriate to ask a patient to refrain from treating an attack in order to determine severity.

The panellists discussed some examples of criteria identified by CADTH from international jurisdictions (summarized in Appendix 3) and indicated that these are problematic and not aligned with Canadian clinical practice. In particular, they commented on the following policies:

- The National Health Service (NHS) England 2016 Clinical Commissioning Policy for C1-INH concentrate for LTP of C1-INH HAE requires that, for LTP with C1-INH concentrate to be funded, patients must experience two or more clinically significant attacks per week despite oral prophylaxis (unless contraindicated) (see Appendix 3).[35] Panel members commented that applying this criterion means that a patient would have to be very symptomatic before initiating LTP with C1-INH concentrate.
- The Australian Medical Services Advisory Committee (MSAC) advised in 2015 that LTP with C1-INH concentrate was only justified from a cost-effectiveness perspective for patients with at least eight attacks per month without LTP (Appendix 3).[36] The panellists indicated that such a patient would already be using on-demand therapy twice a week and would effectively be on LTP but with their attacks not being appropriately controlled.
- The panellists further mentioned that, although the NHS Commissioning Policy[35] defines the term "clinically significant attack," the definition mentions "severe abdominal pain which will not respond to oral analgesia" as a potential cause of pain or disability that disrupts normal activities. However, the panellists believe that response to oral analgesia should not be a consideration, as such attacks should be treated with an C1-INH HAE therapy and any analgesia would be adjunctive.

Treatment History

There was agreement among the panellists that a patient's condition should not be required to fail oral LTP treatment in order for the patient to have access to C1-INH concentrate or lanadelumab for LTP. In addition to the considerations already discussed regarding oral LTP, panellists mentioned that danazol is not indicated for the treatment of C1-INH HAE and there is currently a shortage of danazol in Canada. Antifibrinolytics are not well tolerated and are not effective. The 2014 Canadian guideline[1] specifies that a patient's condition should not need to fail other LTP therapies before LTP with C1-INH concentrate is considered.

With regard to medications known to cause angioedema, these medications would be eliminated as part of the standard management of patients with C1-INH HAE and there is no need to specify this as a criterion for the initiation of LTP with C1-INH concentrate or lanadelumab.

Least Suitable Patients

The panellists agreed that asymptomatic patients and patients with mild and/or infrequent C1-INH HAE attacks would be least suitable for LTP with C1-INH concentrate or lanadelumab. Short-term prophylaxis with C1-INH concentrate can be used in such patients if they are undergoing surgery or in other situations known to trigger C1-INH HAE attacks. LTP with C1-INH concentrate or lanadelumab is not suitable for patients who are unwilling to perform the injections or do not have a support system to assist them with the required injections. In addition, patients without a confirmed diagnosis of C1-INH HAE 1 or C1-INH HAE would not be suitable for LTP of acute attacks with C1-INH concentrate or lanadelumab. It is not known if patients with HAE-nC1INH would benefit from C1-INH concentrate or lanadelumab LTP, and their suitability is currently unclear. Lanadelumab would not be used in patients under 12 years old (except in cases where there is no other option) or in patients who are pregnant. The panellists also noted there will always be some patients who are nonadherent with their therapies, though nonadherence to one therapy does not render a patient unsuitable for a different therapy.

Assessment of Response to Treatment

Response would be determined by a reduction in frequency or severity of symptoms, as well as an improvement in quality of life and the ability to perform activities of daily living. The panellists noted that the clinical significance of a reduction in attack frequency must be interpreted in the context of other factors, particularly attack severity and use of rescue medication (on-demand treatment), though there may be instances in which a reduction in attack frequency and/or severity is clinically meaningful despite no change in the use of rescue medication.

Being able to return to a normal life is also important for patients. Patients may be differentially impacted by a reduction in attacks based on what their normal work or school life and activities were prior to the onset of C1-INH HAE; therefore, it is difficult to assess or measure response in terms of ability to perform activities of daily living, since patients tend to modify their activities in response to their disability. A reduction in visits to the emergency department or in hospitalizations would also be relevant, though such outcomes are not typically assessed in clinical trials.

The panellists considered a follow-up period of three to six months after treatment initiation to be reasonable and in alignment with how often clinicians currently see their patients with C1-INH HAE in Canadian practice, with the acknowledgement that it may be more likely for clinicians to see their patients every six months. Recent attack frequency or severity are typically assessed in the clinic by simply asking the patient. In clinical trials, patients recorded attack onset, duration, severity, and resolution in a diary. Since frequency of C1-INH HAE attacks can vary in the short term, attacks should be assessed by evaluating attacks that occur over a period of at least one month. Assessing response to therapy generally involves having a discussion with the patient.

Treatment Adjustments

According to the panellists, the dose or frequency of dosing of C1-INH concentrate can be increased if a patient's attacks are not well controlled on the starting dosage regimen. Patients who continue to experience C1-INH HAE attacks on LTP with SC C1-INH concentrate may be switched to LTP with IV C1-INH concentrate to facilitate the administration of larger volumes. If improvements are not seen with these adjustments, patients could switch to lanadelumab, if available.

Alternatively, some patients on the maximum dose of C1-INH concentrate could have add-on therapy with a low-dose androgen. The panellists noted that combination therapy with C1-INH concentrate and lanadelumab would generally not be considered for LTP, given the clinical trial results for lanadelumab and the availability of effective therapies for on-demand treatment. They estimated that the combination of C1-INH concentrate and lanadelumab for LTP would be used in less than 5% to 10% of patients with C1-INH HAE. Patients would most likely switch to LTP with C1-INH concentrate if lanadelumab was not effective.

If a patient were attack-free for six to 12 months on a stable regimen, a dose reduction or reduction in dose frequency could be considered for C1-INH concentrate and, potentially, lanadelumab.

Treatment Discontinuation

The panellists indicated that patients may titrate their LTP therapy downward and trial discontinuation can be considered for a stable patient who has access to on-demand treatment. However, based on the panellists' clinical experience, it is rare to completely discontinue LTP even in a stable patient due to lack of experience with discontinuation and the potential consequences if the patient does not remain stable.

It is possible for some patients to go into remission and, potentially, these patients could discontinue LTP. This may be more likely in patients who have acquired angioedema; for example, LTP for HAE may be discontinued following treatment of the underlying malignancy.

According to the panellists, lanadelumab would be discontinued for patients who become pregnant.

Prescribing Conditions

Patients with HAE are diagnosed, treated, and monitored by hematologists or clinical immunologists/allergists. Hospital privileges and access to a blood bank are required to be able to prescribe C1-INH concentrate.

Additional Considerations

Due to dependency on plasma and the risk of shortages of these products, it is very important to have choice and flexibility in available therapies for LTP for the prevention of C1-INH HAE attacks.

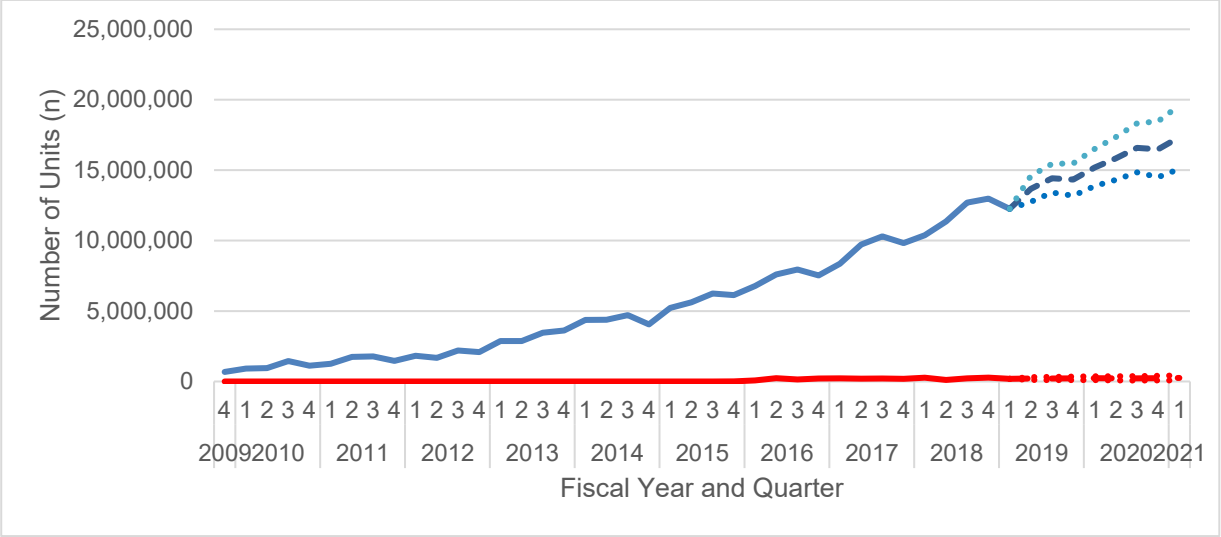
With respect to additional professional resources, the panellists noted that the Canadian Hereditary Angioedema Network, a network of physicians who treat HAE, would be positioned to assess or issue recommendations or to review indications, but not to assess individual prescriptions.

Utilization Data Analysis

National Utilization and Spending

Over the 10-year observational period, the total number of C1-INH concentrate units distributed by CBS per quarter increased 18-fold from 679,000 units in Q4 2009 to 12,444,000 units in Q2 2019 (figures 4 and 5). Berinert was the most distributed nationally of the two C1-INH concentrate products in 2018, representing [redacted] of total units compared with [redacted] of Cinryze. Total utilization exhibited a sharp growth throughout the entirety of the observation period, growing on average 36% from year to year. The sharpest growth occurred in 2013, when average annual growth grew to 64%. We forecast that use will continue to grow for both products and will grow to [redacted] units of Berinert and [redacted] units of Cinryze distributed nationally over all four quarters combined in 2020, representing a growth of 35% for Berinert and 5% for Cinryze.

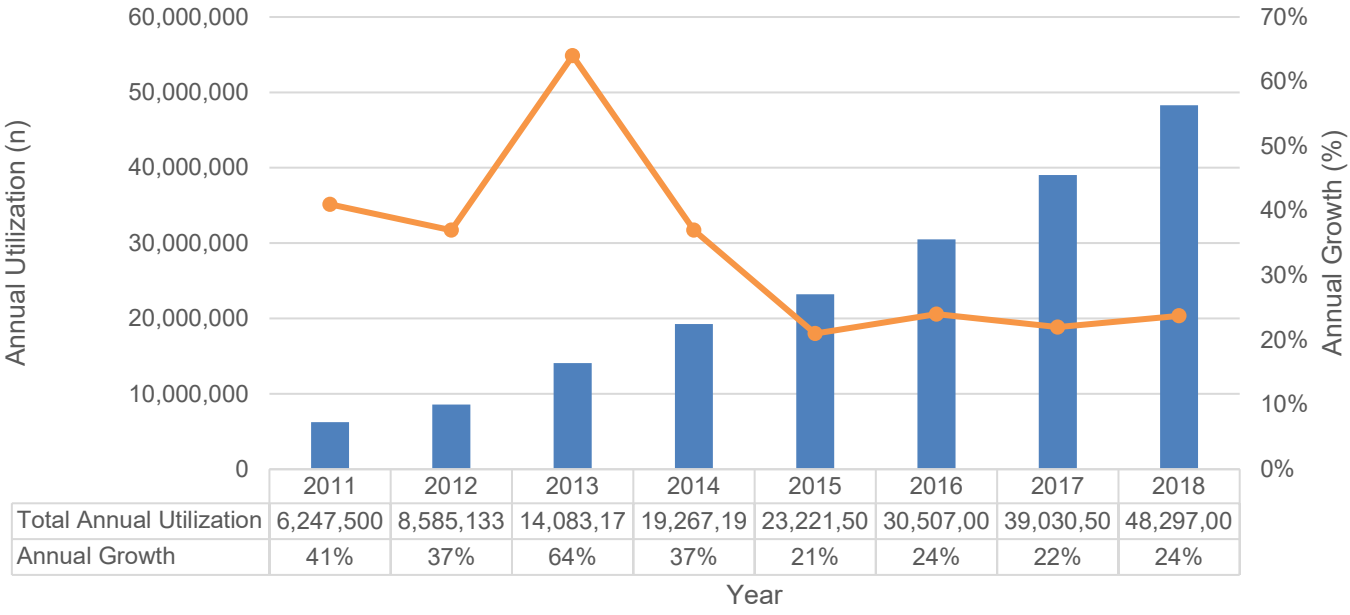
Figure 4: Total Units of C1-Esterase Inhibitors Distributed by Canadian Blood Services From 2009 to 2018, Forecasted 2019 to 2021



Note: The fiscal year for Canadian Blood Services is April 1 to March 31; therefore, Q1 is April to June, Q2 is July to September, Q3 is October to December, and Q4 is January to March.

Legend: The blue line depicts the utilization of Berinert, and the red line depicts the utilization of Cinryze. Confidence intervals are represented as dotted lines.

Figure 5: Total Annual Units and Annual Year-Over-Year Growth of C1-Esterase Inhibitors Distributed by Canadian Blood Services From 2011 to 2018



	2011	2012	2013	2014	2015	2016	2017	2018
Total Annual Utilization	6,247,500	8,585,133	14,083,17	19,267,19	23,221,50	30,507,00	39,030,50	48,297,00
Annual Growth	41%	37%	64%	37%	21%	24%	22%	24%

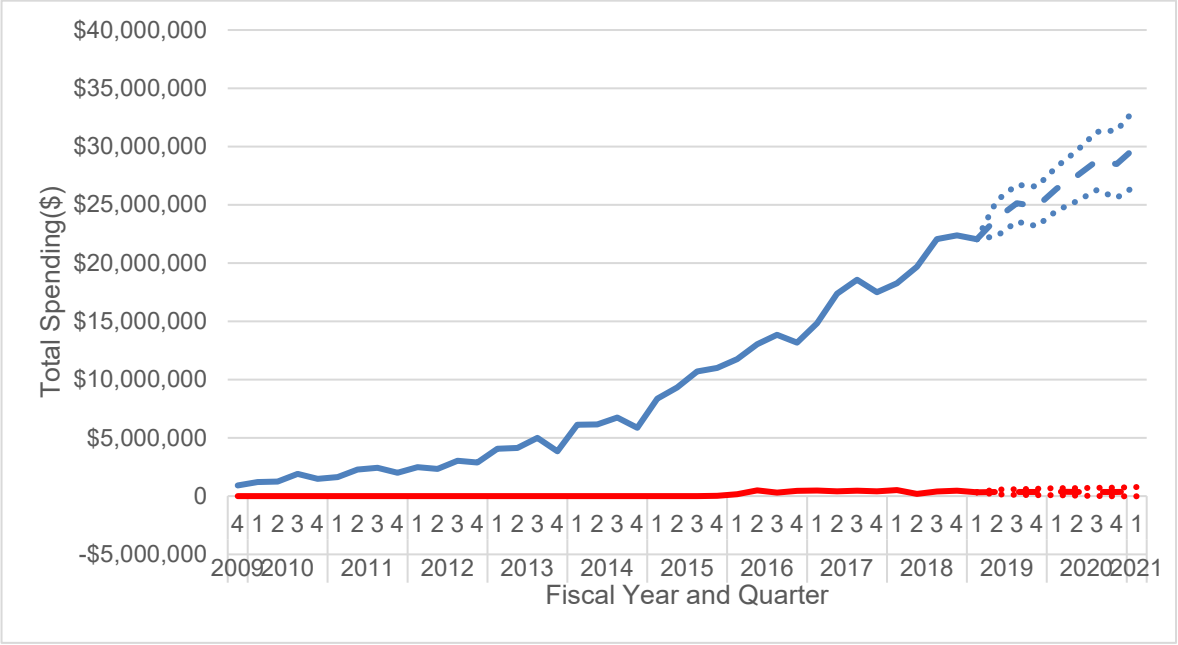
Year

Note: The fiscal year for Canadian Blood Services is April 1 to March 31; therefore, Q1 is April to June, Q2 is July to September, Q3 is October to December, and Q4 is January to March.

Legend: Orange line represents annual growth.

Similar trends were observed for total spending over the same 10-year observation period. The total cost of C1-INH concentrate units distributed per quarter increased 24-fold from $915,000 in Q4 2009 to $22,370,000 in Q2 2019 (figures 6 and 7). Of the two drug products, Berinert accounted for the highest total spending nationally in 2018, representing [redacted] of total expenditures compared with only [redacted] for Cinryze. Total spending on C1-INH concentrate products also exhibited sharp growth throughout the entirety of the study period, growing on average 43% from year to year. The sharpest annual growth in total expenditure occurred in 2013 when it grew to 59%, and this aligns with the first year that Cinryze was distributed in Canada. Based on this continued growth, it is forecast that, by 2020, spending will grow to [redacted] for Berinert and remain around [redacted] for Cinryze, a growth of 35% for Berinert.

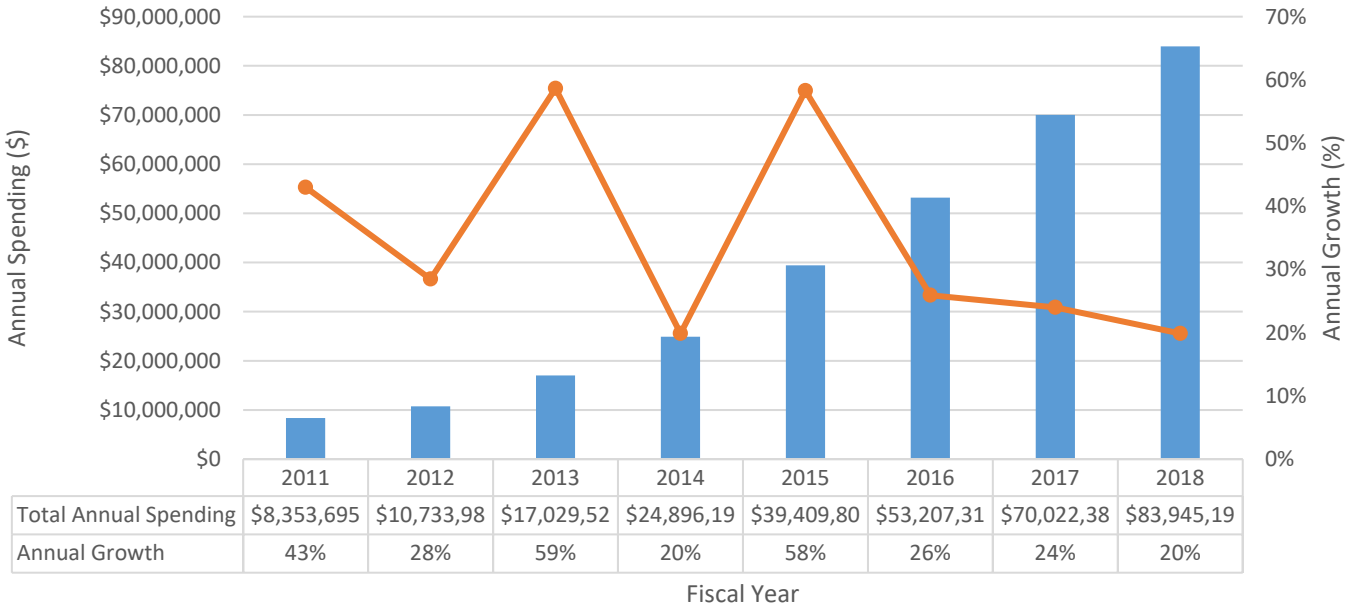
Figure 6: Total Spending on C1-Esterase Inhibitors Distributed by Canadian Blood Services From 2009 to 2018, Forecasted for 2019 to 2021



Note: The fiscal year for Canadian Blood Services is April 1 to March 31; therefore, Q1 is April to June, Q2 is July to September, Q3 is October to December, and Q4 is January to March.

Legend: The blue line depicts the utilization of Berinert, and the red line depicts the utilization of Cinryze. Confidence intervals are represented as dotted lines.

Figure 7: Total Annual Spending and Annual Growth of Spending on C1-Esterase Inhibitors Distributed by Canadian Blood Services From 2011 to 2018



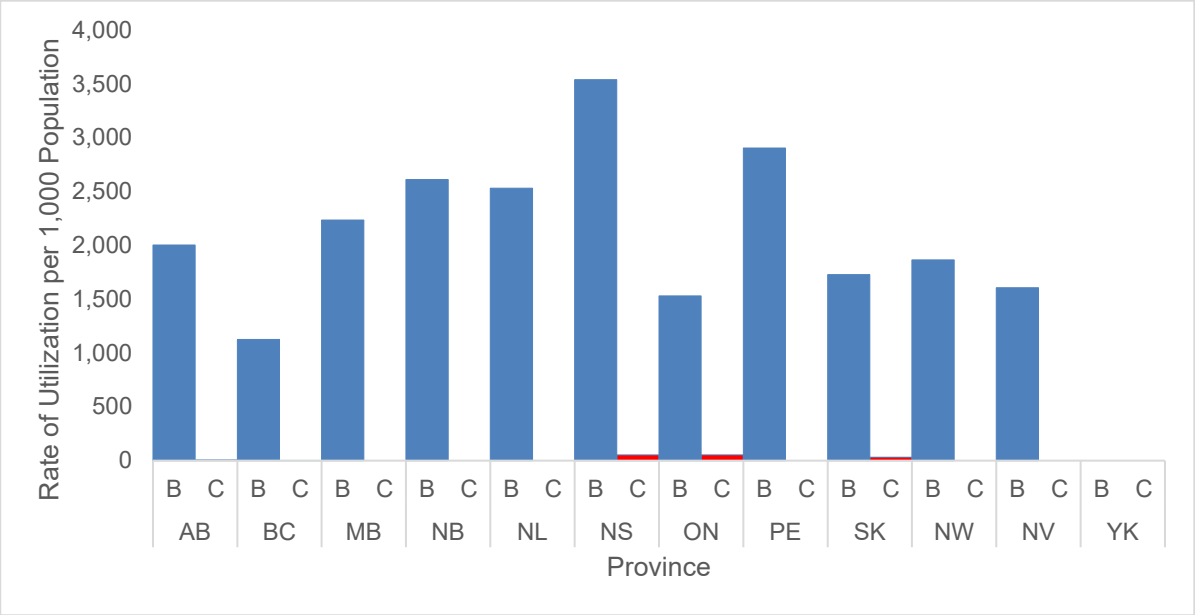
	2011	2012	2013	2014	2015	2016	2017	2018
Total Annual Spending	$8,353,695	$10,733,98	$17,029,52	$24,896,19	$39,409,80	$53,207,31	$70,022,38	$83,945,19
Annual Growth	43%	28%	59%	20%	58%	26%	24%	20%

Note: The fiscal year for Canadian Blood Services is April 1 to March 31; therefore, Q1 is April to June, Q2 is July to September, Q3 is October to December, and Q4 is January to March.

Jurisdictional Utilization and Spending

A greater than three-fold difference in the distribution of C1-INH concentrate products was observed between the jurisdictions; the highest utilization rate occurred in Nova Scotia (3,592 units per 1,000 people), while the lowest utilization rate was observed in British Columbia (1,127 units per 1,000 people [Figure 8 and Table 12]). Provinces with distribution rates below the national rate (1,720 units per 1,000 people) included British Columbia, Ontario, and Nunavut. No units were distributed in Yukon in 2018. Similar observations were made for spending, with the highest rate occurring in Nova Scotia ($6,240 per 1,000 people) and lowest rate in British Columbia ($1,958 per 1,000 people). Provinces with cost rates below the national rate ($2,989 per 1,000 people) included British Columbia, Ontario, and Nunavut. Although the spending rate was not the highest, the largest proportion of units was distributed to Ontario (47%; 22,488,000 units) and Alberta (18%; 8,616,500 units), accounting for nearly two-thirds of all units distributed.

Figure 8: Rate of Utilization of C1-Esterase Inhibitors Distributed by Canadian Blood Services by Jurisdiction in Calendar Year 2018



B = Berinert; C = Cinryze.

Table 12: Total Units, Total Cost, and Rate of Utilization and Spending by Jurisdiction in 2018

		Utilization (Units)	Rate of Utilization[a]	Total Product Cost ($)	Rate of Spending ($)[a]
Alberta	Berinert	8,586,500	2,003	[redacted]	3,481
	Cinryze	30,000	7	[redacted]	12
British Columbia	Berinert	5,424,500	1,126	[redacted]	1,957
	Cinryze	4,000	1	[redacted]	1
Manitoba	Berinert	2,990,000	2,234	[redacted]	3,879
	Cinryze	0	0	[redacted]	0
New Brunswick	Berinert	1,380,500	2,611	[redacted]	4,535
	Cinryze	0	0	[redacted]	0
Newfoundland and Labrador	Berinert	1,332,500	2,531	[redacted]	4,400
	Cinryze	0	0	[redacted]	0
Nova Scotia	Berinert	3,376,000	3,539	[redacted]	6,144
	Cinryze	51,000	53	[redacted]	95
Ontario	Berinert	21,726,000	1,531	[redacted]	2,660
	Cinryze	762,000	54	[redacted]	95
Prince Edward Island	Berinert	441,500	2,904	[redacted]	5,059
	Cinryze	0	0	[redacted]	0
Saskatchewan	Berinert	2,011,500	1,728	[redacted]	3,006
	Cinryze	37,000	32	[redacted]	57
Northwest Territories	Berinert	83,000	1,864	[redacted]	3,213
	Cinryze	0	0	[redacted]	0

		Utilization (Units)	Rate of Utilization[a]	Total Product Cost ($)	Rate of Spending ($)[a]
Nunavut	Berinert	61,000	1,605	[redacted]	2,816
	Cinryze	0	0	[redacted]	0
Yukon	Berinert	0	0	[redacted]	0
	Cinryze	0	0	[redacted]	0

[a] Rate reported per 1,000 people.

User-level Insights from British Columbia

Over the 10-year observational period, the total number of C1-INH concentrate users per quarter increased four-fold from nine units in Q1 2009 to 42 units in Q2 2019 (Figure 9). The proportion of new users decreased over time from 44% (n = 5) in Q1 2019 to 14% (n = 36) in Q1 2019. The average number of units per user exhibited sharp growth, growing five-fold, throughout the entirety of the observation period, growing from 5,000 units per user in Q1 2009 to 31,583 per user in Q1 2019 (Figure 10). The rate of use appears to have shifted most significantly in 2014, growing from an average of 10,893 units per user in 2013 to 15,403 units per user in 2014.

Figure 9: Number of Individuals Receiving C1-Esterase Inhibitors Distributed by Canadian Blood Services in British Columbia and Yukon by Quarter From 2009 to 2019

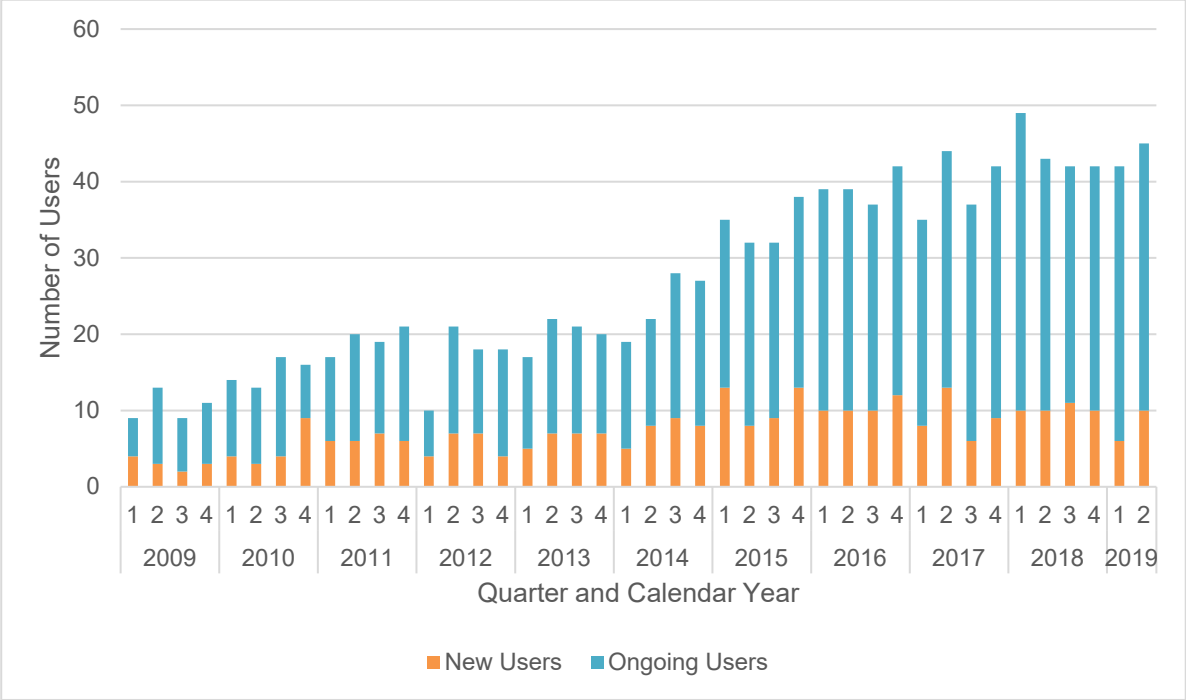
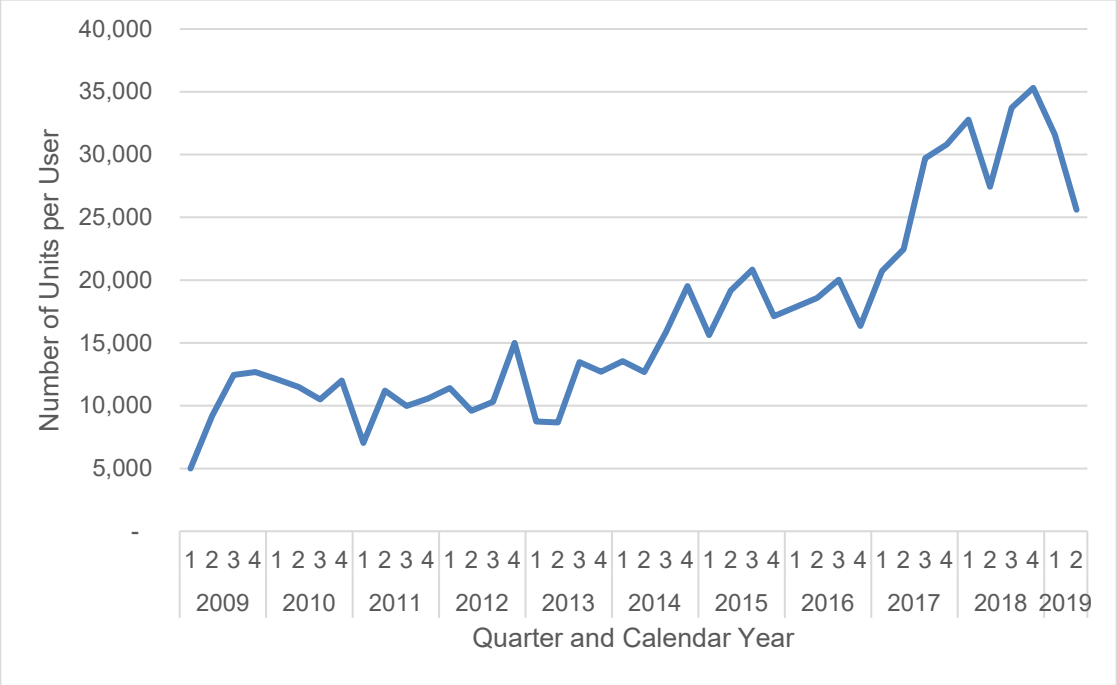


Figure 10: Average Number of Units per User of C1-Esterase Inhibitors Distributed by Canadian Blood Services in British Columbia and Yukon by Quarter From 2009 to 2019



Economic Evaluation

Base-Case Results

The results of the CADTH base-case analysis, with the revisions described previously, are presented sequentially. All results are based on a probabilistic analysis.

The “no LTP” strategy was the reference intervention, given it had the lowest expected costs. The average total lifetime total costs for no LTP was $9,172,106, whereas the average lifetime total costs for patients receiving LTP was $9,827,239 for Cinryze, $17,363,457 for lanadelumab, and $24,468,170 for Berinert. Detailed cost results can be found in Table 27. Lifetime QALYs were 22.5573, 23.5299, 24.1099, and 24.0993 for no LTP, Cinryze, lanadelumab, and Berinert, respectively. Berinert was dominated by lanadelumab, which means lanadelumab was associated with lower total costs and higher QALYs compared with Berinert. The sequential ICURs were $673,632 per QALY gained for Cinryze compared with no LTP, and $12,992,477 per QALY gained for lanadelumab compared with Cinryze (Table 13). Additionally, lanadelumab had a pairwise ICUR of $5,275,949 compared with no LTP; whereas Berinert had a pairwise ICUR of $9,919,626 compared with no LTP. The cost-effectiveness acceptability curve and scatterplot can be found in Figure 11 and Figure 12, respectively. Where a decision-maker is willing to pay between $50,000 and $2,000,000 per QALY gained, Cinryze had the highest probability of being cost-effective.

Table 13: CADTH Base-Case Analyses

Therapy	Expected Costs ($)	Expected QALYs	Incremental Costs ($)	Incremental QALYs	Pairwise ICUR (Versus No LTP), $/QALY Gained ($)	Sequential ICUR, $/QALY Gained ($)
No LTP	9,172,106	22.5573				
Cinryze	9,827,239	23.5299	655,133	0.9725	673,632	673,632
Lanadelumab	17,363,457	24.1099	7,536,218	0.5800	5,275,949	12,992,477
Berinert	24,468,170	24.0993	7,104,713	−0.0106	9,919,626	Dominated

ICUR = incremental cost-utility ratio; LTP = long-term prophylaxis; QALY = quality-adjusted life-year.

Scenario Analysis Results

Including Haegarda as Comparator

Since Haegarda is still not marketed in Canada, there is no publicly available drug cost for this therapy, and it was not included as a comparator in the base-case analysis. It was, however, included as a comparator in an exploratory analysis. In this analysis, the costs for Haegarda were derived from a model submitted by the supplier to CBS. In the exploratory analysis, Haegarda was dominated by lanadelumab, i.e., lanadelumab was associated with lower total costs and higher QALYs compared with Haegarda, whereas Berinert was dominated by Haegarda. The results of the exploratory analysis are presented sequentially in Table 14.

Table 14: CADTH Exploratory Analyses – Inclusion of Haegarda as Comparator

Therapy	Expected Costs ($)	Expected QALYs	Incremental Costs ($)	Incremental QALYs	Pairwise ICUR (Versus No Prophylaxis), $/QALY Gained ($)	Sequential ICUR, $/QALY Gained ($)
No prophylaxis	9,172,106	22.5573				
Cinryze	9,827,239	23.5299	655,133	0.9725	673,632	673,632
Lanadelumab	17,363,457	24.1099	7,536,218	0.5800	5,275,949	12,992,477
Haegarda	18,632,629	24.1047	1,269,172	−0.0052	6,114,058	Dominated
Berinert	24,468,170	24.0993	5,835,541	−0.0054	9,919,626	Dominated

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

CADTH explored an alternative price scenario for Haegarda. In a scenario in which the cost of Haegarda is equal to the cost of Cinryze (the LTP treatment with the lowest cost), Haegarda was the lowest-cost treatment, Cinryze, Berinert, and no LTP were dominated, and lanadelumab was associated with an ICUR of $1,225,384,912. Results can be found in Table 28.

Due to the lack of information on the true costs for Haegarda, the results of this exploratory analysis should be interpreted with caution.

Alternative Dosing Berinert

In the base case, Berinert is assumed to be used subcutaneously at a 60 IU/kg dose as LTP. As per clinical expert feedback, a proportion of patients (ranging from 10% to 25%) may use Berinert intravenously as LTP at a dose of 20 IU/kg. CADTH further explored this scenario and found that if 10% to 25% of patients receive Berinert IV LTP at a dose of 20 IU/kg, then Berinert would continue to be dominated by lanadelumab. At a higher uptake of Berinert IV for LTP of 50%, Berinert would be associated with an ICUR of $12,131,111

compared with Cinryze, whereas lanadelumab would be associated with an ICUR of $123,543,779 compared with Berinert when used for LTP (Table 29).

Baseline Attack Rates Scenario Analyses

CADTH explored the impact of alternative baseline attack rates by varying the baseline attack rate from one to 10 attacks per month and holding all other parameters constant, as per the ICER report. CADTH found there was no attack rate (between one and 10 per month) that would allow lanadelumab or Berinert to reach cost-effectiveness thresholds of $50,000 to $150,000 per QALY. An attack rate of 9.6, 9.3, and 9.1 per month would allow Cinryze to reach cost-effectiveness thresholds of $50,000, $100,000, and $150,000 per QALY, respectively (Figure 13).

CADTH further explored the impact of assuming mild, moderate, and severe attacks take the same time to resolve, i.e., 48 hours if treated and 72 hours if untreated, as per the clinical expert feedback. This analysis resulted in an ICUR of $284,233 per QALY gained for Cinryze compared with no LTP, and $9,470,001 per QALY gained for lanadelumab compared with Cinryze. Berinert was dominated by lanadelumab (Table 30).

Threshold Analysis: Long-Term Prophylaxis Treatment Costs

CADTH performed threshold analyses by altering the price of the LTP treatments to estimate the maximum prices required to achieve WTP thresholds of $50,000, $100,000, $150,000, $200,000, $300,000, and $500,000 per QALY. Threshold prices are shown in Table 32 and ranged from [redacted] to [redacted] for Cinryze, $3,764 to $4,653 for lanadelumab, and [redacted] to [redacted] for Berinert. These prices correspond to a price reduction of 62% to 70% for Cinryze, 77% to 82% for lanadelumab, and 84% to 87% for Berinert.

Alternative Dosing Lanadelumab

A reduction in the dosing frequency to every four weeks in patients who were attack-free on lanadelumab for six months was explored. In the HELP-03 study, 44% of patients on the "every two weeks" regimen and 31% of patients on the "every four weeks" regimen achieved attack-free status. Therefore, CADTH assumed that dosing every four weeks would be attempted in 44% of patients, with only 31% remaining attack-free on this dosing at six months and beyond. This is the same approach taken by ICER, as data from the HELP-03 study is the only clinical data available on alternative dosing of lanadelumab. In this analysis, lanadelumab was associated with an ICUR of $5,275,139 compared with no LTP (Table 31). CADTH conducted threshold analyses on the proportion of patients who could switch to a lanadelumab dosing frequency of every four weeks and found that there is no percentage of patients who could switch to dosing every four weeks that would make lanadelumab cost-effective at the $150,000 WTP threshold.

Societal Perspective (Including Direct Health Care Costs and Indirect Patient Costs)

Productivity costs, including lost wages for patients and out-of-pocket expenses for acute attacks, were included in an exploratory analysis. Due to the lack of Canadian-specific data on indirect costs for acute attacks, indirect costs were estimated from a US study on the economic costs associated with acute attacks and long-term management of C1-INH HAE.[37] Indirect costs included missed workdays and patient-reported out-of-pocket expenses for child care and travel. Costs were converted to Canadian dollars; per-attack indirect costs of $58 for mild, $247 for moderate, and $492 for severe attacks were included in the analysis. The average total lifetime direct and indirect costs for no LTP was $9,427,431, whereas the average lifetime direct and indirect costs for patients receiving LTP was $9,945,157 for

Cinryze, $17,367,203 for lanadelumab, and $24,457,334 for Berinert. Detailed cost results can be found in Table 34. From a societal perspective, Cinryze had an ICUR of $533,392 compared with no LTP, whereas lanadelumab had an ICUR of $12,762,387 compared with Cinryze; Berinert was dominated by lanadelumab. Since the societal costs of C1-INH HAE are small relative to the total health care costs, the societal-perspective analysis resulted in ICURs similar to the base-case analysis.

A summary of the results of the exploratory analyses can be found in Table 15; detailed results can be found in Table 28 to Table 34 (Appendix 4).

Table 15: CADTH Reanalysis and Exploratory Analyses Results

Scenario	Treatments	Total Costs ($)	Total QALYs	Sequential ICUR ($ per QALY) ($)
CADTH base case	No LTP	9,172,106	22.5573	–
	Cinryze	9,827,239	23.5299	673,632
	Lanadelumab	17,363,457	24.1099	12,992,477
	Berinert	24,468,170	24.0993	Dominated
CADTH base case + inclusion of Haegarda (cost submitted by CBS)	No LTP	9,172,106	22.5573	–
	Cinryze	9,827,239	23.5299	673,632
	Lanadelumab	17,363,457	24.1099	12,992,477
	Haegarda	18,632,629	24.1047	Dominated
	Berinert	24,468,170	24.0993	Dominated
CADTH base case + inclusion of Haegarda (cost equal to Cinryze)	Haegarda	8,704,659	24.1376	–
	No LTP	9,164,753	22.5908	Dominated
	Cinryze	9,818,926	23.5649	Dominated
	Lanadelumab	17,336,485	24.1447	1,225,384,912
	Berinert	24,479,847	24.1006	Dominated
CADTH base case + inclusion of Haegarda (cost equal to Berinert) **90% of patients receive off-label Berinert subcutaneously (60 IU/kg dose); 10% receive it intravenously (20 IU/kg dose)**	No LTP	9,169,712	22.5876	–
	Cinryze	9,818,180	23.5613	665,975
	Lanadelumab	17,356,894	24.1381	13,070,542
	Berinert	22,937,218	24.1354	Dominated
CADTH base case + inclusion of Haegarda (cost equal to Berinert) **75% of patients receive off-label Berinert subcutaneously (60 IU/kg dose); 25% receive it intravenously (20 IU/kg dose)**	No LTP	9,168,757	22.5606	–
	Cinryze	9,825,101	23.5329	675,046
	Lanadelumab	17,339,038	24.1123	12,968,943
	Berinert	20,664,537	24.1054	Dominated
CADTH base case + inclusion of Haegarda (cost equal to Berinert) **50% of patients receive off-label Berinert subcutaneously (60 IU/kg dose); 50% receive it intravenously (20 IU/kg dose)**	No LTP	9,166,163	22.5807	–
	Cinryze	9,820,662	23.5527	673,300
	Berinert	16,779,605	24.1264	12,131,111
	Lanadelumab	17,351,916	24.1310	123,543,779
CADTH base case + mild, moderate, and severe attacks take 48 hours to resolve if treated, 72 hours if untreated	No LTP	9,163,495	21.8961	–
	Cinryze	9,553,404	23.2679	284,233
	Lanadelumab	17,146,869	24.0697	9,470,001
	Berinert	24,068,607	24.0643	Dominated

Scenario	Treatments	Total Costs ($)	Total QALYs	Sequential ICUR ($ per QALY) ($)
CADTH base case + alternative dosing for lanadelumab	No LTP	9,176,195	22.5656	–
	Cinryze	9,821,157	23.5385	662,904
	Lanadelumab	17,368,110	24.1185	13,012,114
	Berinert	24,439,064	24.0922	Dominated
CADTH + societal perspective	No LTP	9,427,431	22.6003	–
	Cinryze	9,945,157	23.5709	533,392
	Lanadelumab	17,367,203	24.1525	12,762,387
	Berinert	24,488,470	24.1227	Dominated

CBS = Canadian Blood Services. ICUR = incremental cost-utility ratio; LTP = long-term prophylaxis; QALY = quality-adjusted life-year.

Budget Impact Analysis

Base-Case Results

In the current year, for the reference scenario, it is estimated that the budget impact in Canada of Berinert, Cinryze, and icatibant is $81,681,027. Results are presented in Table 16.

Table 16: Current Year Estimates, Reference Scenario

	Cost A: Patients Requiring LTP ($)	Cost B: Patients Not Requiring LTP ($)	Total Costs (A + B) ($)
LTP therapy costs	68,742,698	0	68,742,698
On-demand therapy costs	4,056,832	8,881,497	12,938,329
Total drug costs	72,799,530	8,881,497	81,681,027

LTP = long-term prophylaxis.

Table 17 summarizes the total annual drug costs and BIA of introducing new therapies (Haegarda and lanadelumab) for LTP of C1-INH HAE. Over three years, introducing new drugs will cost $226,536,105. As a result, in patients who require LTP, Haegarda and lanadelumab becoming available is estimated to result in cost savings of $3,908,698 in year 1, $5,308,464 in year 2, and $9,289,813 in year 3, compared with using currently funded treatments only, i.e., Berinert and Cinryze. Over three years, compared with the reference scenario, this results in a total estimated cost savings of $18,506,975.

Table 17: Budget Impact Analysis Results for New-Drug Scenario

Annual Cost Outcomes	Reference Scenario			New-Drug Scenario		
	Year 1 ($)	Year 2 ($)	Year 3 ($)	Year 1 ($)	Year 2 ($)	Year 3 ($)
LTP	68,742,698	68,742,698	68,742,698	65,388,437	34,234,476	60,853,309
On-demand therapy	12,938,329	12,938,329	12,938,329	12,383,892	12,138,086	11,537,905
Total drug costs	81,681,027	81,681,027	81,681,027	77,772,329	76,372,562	72,391,214
Budget impact	**Reference**	**Reference**	**Reference**	**−3,908,698**	**−5,308,464**	**−9,289,813**

LTP = long-term prophylaxis.

Note: Negative values denote cost savings.

As an exploratory analysis, CADTH compared two additional budget scenarios: a reference scenario where patients are treated only with on-demand therapies and do not receive LTP; and an LTP scenario, where patients requiring LTP receive LTP with currently available therapies (Berinert or Cinryze). Providing LTP results in estimated additional costs of

$56,882,033 in years 1, 2, and 3 (Table 18). Over three years, providing LTP results in a total estimated cost of $170,646,098 compared with not providing LTP to patients requiring LTP.

Table 18: Budget Impact Analysis Results for No Long-Term–Prophylaxis Scenario, Current Long-Term Prophylaxis Treatments Only (Berinert, Cinryze)

Annual Cost Outcomes	No-Prophylaxis Scenario			Prophylaxis Scenario		
	Year 1 ($)	Year 2 ($)	Year 3 ($)	Year 1 ($)	Year 2 ($)	Year 3 ($)
LTP therapy	0	0	0	68,493,449	68,493,449	68,493,449
On-demand therapy	24,557,552	24,557,552	24,557,552	12,946,136	12,946,136	12,946,136
Total drug costs	24,557,552	24,557,552	24,557,552	81,439,585	81,439,585	81,439,585
Budget impact	**Ref**	**Ref**	**Ref**	**56,882,033**	**56,882,033**	**56,882,033**

LTP = long-term prophylaxis; ref = reference.

Note: Negative values denote cost savings.

Scenario Analysis Results

A summary of the results of the exploratory analyses can be found in Table 19. These results reflect analyses that provided the greatest influence on BIA results. Detailed results of scenario and sensitivity analyses can be found in Table 38 to Table 43 (Appendix 5).

Table 19: CADTH Analysis and Select Exploratory Analysis Results

	Base-Case Value	Scenario Analysis Estimate	Total Costs: Current Year ($)	3-Year Total: New-Drug BIA ($)	3-Year Total: No-LTP BIA ($)
Base Case			81,681,027	−18,506,975	170,646,098
Prevalence scenarios	**1:67,000**	**1:10,000**	547,262,879	−123,996,732	1,143,328,855
		1:35,000	156,360,823	−35,427,638	326,665,387
		1:50,000	109,452,576	−24,799,346	228,665,771
		1:92,000	59,485,096	−13,477,906	124,274,876
Percentage of patients Diagnosed	**65%**	**85%**	106,813,650	−24,201,429	223,152,589
		100%	125,663,118	−28,472,269	262,532,458
Percentage of HAE patients requiring LTP	**41%**	**60%**	112,186,236	−26,985,178	249,725,997
		80%	144,551,132	−35,980,238	332,967,996
		100%	176,916,028	−44,975,297	416,209,994
Percentage of patients using Berinert SC for LTP	**75%**	**100%**	93,292,420	−34,762,926	205,353,976
		50%	70,069,633	−2,251,024	135,938,220
Berinert SC dose	**60 IU/kg**	**40 IU/kg**	64,263,936	5,876,952	118,584,281
Baseline attack frequency: those requiring LTP	**3.39**	**5**	83,607,723	−19,815,445	154,102,399
New-drug uptake scenarios	Haegarda: [redacted] Lanadelumab: [redacted]	**Only Haegarda enters**	81,681,027	−9,408,490	NA
		Only lanadelumab enters	81,681,027	−9,098,485	NA
		Haegarda replaces all Berinert LTP[a]	81,681,027	−67,476,001	NA

BIA = budget impact analysis; HAE = hereditary angioedema; LTP = long-term prophylaxis; NA: not applicable; SC = subcutaneous.

Note: Negative values denote cost savings.

[a] In this scenario, there is no change to the current proportion of patients using Cinryze ([redacted]) and no LTP ([redacted]) in years 1, 2, and 3.

Results of sensitivity analyses on the total costs in the current year ranged from $59,485,096 for a low C1-INH HAE prevalence estimate of 1:92,000 to $547,262,879 for a high-prevalence estimate of 1:10,000, demonstrating the BIA's sensitivity to the number of C1-INH HAE patients considered. Using a prevalence of 1:10,000 resulted in cost savings of $123,996,732, while using a prevalence of 1:92,000 resulted in cost savings of $13,477,906 over three years (Table 38). In the no-LTP BIA, the budget impact of providing LTP in the 1:10,000 prevalence scenario was estimated to be more than one billion dollars over three years. In the 1:92,000 prevalence scenario, the budget impact of providing LTP was $124,274,876 over three years.

If a greater percentage of patients are diagnosed, this will result in higher annual costs, as well as greater cost savings from new drugs intended for LTP becoming accessible to patients (Table 39). Similarly, if a greater percentage of patients require access to LTP, this will result in an increase in current annual costs as well as greater costs savings from new drugs becoming accessible to patients (Table 41).

If it is assumed that 100% of patients are using Berinert subcutaneously for LTP of attacks, and no patients are using it intravenously, there will be greater cost savings by introducing new drugs; these savings will mainly result from the difference in Berinert dosing requirements between the IV and SC routes of administration. Conversely, if more patients are using Berinert intravenously for LTP, then the cost savings associated with introducing new therapies will be reduced (Table 42). Across all scenarios, the only scenario where introducing new drugs did not result in cost savings was the scenario where it was assumed that patients using SC Berinert for LTP will use a lower (40 IU/kg) dose.

Finally, CADTH explored the uptake of new drugs and found that the three-year budget impact of introducing new LTP therapies resulted in estimated savings of $9,408,485 to $102,310,181. The scenario that resulted in the greatest cost savings occurred when Haegarda replaced all uses of Berinert SC LTP (Table 43).

Discussion

This project was undertaken to help inform policy work on therapies used for LTP of C1-INH HAE attacks. Four key components were part of this project. The results from each of these components were presented in preceding sections; this section discusses the key implications of these results.

Clinical Expert Consultation

The panel of clinical experts convened by CADTH discussed the following issues:

- How is LTP for the prevention of C1-INH HAE attacks currently used in Canadian clinical practice?
- What are the characteristics of patients who are most likely to benefit from LTP with C1-INH or lanadelumab to prevent C1-INH HAE attacks?
- How are the patients who are most likely to benefit from LTP identified in Canadian clinical practice?

Consultation with the expert panel also provided an opportunity to reflect the general perspective of clinicians caring for patients with C1-INH HAE in this report.

According to the panellists, currently, in Canada, at least half of all patients diagnosed with C1-INH HAE receive LTP for the prevention of acute attacks. Overall, for the routine prevention of attacks, physicians appear to be increasingly using C1-INH concentrate products. This preference by Canadian clinicians is accompanied by decreased use of oral therapies (e.g., danazol or tranexamic acid), which is related to their limited efficacy and associated constraints (e.g., danazol cannot be used in pediatric or pregnant patients) as well as their adverse effects.

Route of administration, dosing frequency, and perceived risk of infection may affect choice of LTP treatment. Given the injectable nature of plasma-derived products, learning how to self-administer these treatments is important for patients wishing to use LTP. In this context, the SC route of administration is generally preferred over the IV route. It may be anticipated that the availability of new therapies intended for SC administration (e.g., Haegarda and lanadelumab) will potentially increase the use of this form of LTP. Also, as lanadelumab is now available in Canada, some patients currently using C1-INH concentrate for LTP, as well as some of the newly diagnosed patients, may opt to switch to lanadelumab, given its more convenient dosing schedule. Other factors considered by physicians when selecting an LTP treatment include availability of scientific evidence, recommendations from guidelines, adverse effects, and perceived risk of infectious agent transmission with blood products. Furthermore, reimbursement of therapies and ease of access (e.g., proximity of a patient to the nearest blood bank) can have an impact on which therapies patients receive for LTP.

Although not available for the clinical expert consultation, the recently updated 2019 International/Canadian Hereditary Angioedema Guideline[4] recommends the use of SC C1-INH concentrate or lanadelumab as first-line therapy for LTP of HAE attacks. It was noted that the level of evidence for this recommendation was consensus due to the lack of direct comparison between LTP therapies; however, there was strong agreement (97.37% agreed).[4] The guideline also recommends that androgens and antifibrinolytics not be used as first-line therapy for LTP.[4] The recommendations regarding LTP in pediatric patients were that C1-INH concentrate (route of administration not specified) is the treatment of choice and that androgens should not be used.[4] These recommendations, which cover issues not

explicitly addressed by recommendations in the 2014 guideline,[1] are generally in line with the results from the clinical expert consultation. For example, the panel indicated that the SC route of administration, either twice a week with C1-INH concentrate or once every two weeks with lanadelumab, is more feasible for patients than IV administration of C1-INH concentrate twice a week.

While the characteristics of patients most likely to benefit from LTP with C1-INH concentrate or lanadelumab were identified by the panel, these characteristics remained relatively broadly defined. Key characteristics would generally include a confirmed diagnosis of C1-INH HAE 1 or C1-INH HAE 2, a higher frequency of attacks, and the presence of severe attacks, such as those which may be debilitating to patients or are life-threatening (e.g., laryngeal involvement). While attack frequency and severity appear to be the main drivers of initiation of LTP with C1-INH concentrate or lanadelumab, the panel did not identify a threshold for attack frequency for identifying patients suitable for these therapies, even if the threshold is applied in conjunction with other criteria. Panel members also indicated that obtaining confirmation of a diagnosis of C1-INH HAE 1 or C1-INH HAE 2 is a feasible requirement, given this diagnosis is standardized across Canada. They also indicated that determining the impact of attacks on the activities of daily living and the health-related quality of life of patients are important considerations, though these are difficult to assess. Other patients who may benefit from LTP are those with a high frequency of hospitalizations or emergency room visits due to acute attacks.

Patients who would be least suitable for LTP with C1-INH concentrate or lanadelumab are those who are asymptomatic, those with mild and/or infrequent C1-INH HAE attacks, those with an unconfirmed diagnosis of C1-INH HAE 1 or C1-INH HAE 2 (there is a lack of evidence supporting the use of LTP in patients with HAE-nC1INH), and those who are unwilling to self-administer these drugs or who do not have a good support system for administering these injections.

With respect to the assessment of the therapeutic response, panellists advised that attack frequency, attack severity, and use of rescue therapies should be evaluated together, rather than in isolation. The assessment should also be done over a period of three to six months after treatment initiation to determine whether the response is clinically meaningful. Options to optimize therapy would include a number of strategies, such as increasing the dose or frequency of C1-INH concentrate and, if improvements are not seen with these adjustments, switching to lanadelumab (assuming coverage is available for this therapy). There was also consensus on the part of experts that failure on oral prophylactic therapies should not be a requirement to access more effective therapies, such as C1-INH concentrate.

Overall, the experts agreed that LTP of C1-INH HAE attacks adds clinical value to the treatment landscape by allowing patients to live a normal life: to work, go to school, perform daily activities, and to participate in recreational and social activities.

The reimbursement recommendation for lanadelumab issued by the CADTH Canadian Drug Expert Committee (and not available at the time of the clinical expert consultation) recommends reimbursing lanadelumab for patients who meet several conditions.[38] In addition to a minimum patient age (12 years) and the requirement of a diagnosis of C1-INH HAE 1 or C1-INH HAE 2, both of which are in line with the clinical expert consultation, the initiation criteria include a threshold for attack frequency: patients must have experienced at least three HAE attacks within any four-week period that required the use of an acute injectable treatment. Renewal criteria were also listed, and patients are to be assessed for response to treatment three months after treatment initiation with lanadelumab, followed by assessment every six months for continued response (generally in line with the clinical expert consultation).

In the reimbursement recommendation, an initial response to treatment would be a reduction from baseline (prior to initiation of lanadelumab) in attack frequency, while continued response would be no increase in attack frequency from baseline. Other conditions for reimbursement are that lanadelumab should not be used in combination with other medications for LTP, and the dosage of lanadelumab should not exceed the Health Canada–approved dosage.

While the panel experts were not able to identify an attack frequency threshold for initiating LTP that could be applied to all patients with HAE, as mentioned previously, the recommendation recently issued by the Canadian Drug Expert Committee for lanadelumab[38] included a threshold of at least three HAE attacks within a four-week period requiring the use of an acute injectable treatment. As noted in one of the discussion points in this recommendation, the mean baseline attack rate for patients in the HELP-03 study for lanadelumab[24] was between three and four per four-week period for each treatment group. Similarly, patients in the COMPACT trial for Haegarda had an overall mean baseline attack rate of 3.3 per month.[25] The policy perspective accounts for the clinical evidence as well as economic, budgetary, and other considerations such as socio-ethical implications and equitable access to therapy. From this perspective, some international public-funding organizations require a higher rate of attacks to be reached before C1-INH concentrate products or lanadelumab can be accessed for the LTP of C1-INH HAE attacks. For example, the NHS England Commissioning Policy for C1-INH concentrate for LTP of C1-INH HAE attacks[35] requires that patients experience at least two clinically significant attacks per week (or approximately eight per month). Also, a threshold of eight attacks per month identified by MSAC was based on a cost-effectiveness perspective.[36]

Utilization Analysis

A drug-utilization study of C1-INH concentrate products Berinert and Cinryze, distributed nationally by CBS, found growing rates of utilization and rising costs over a 10-year time period. Overall, continued growth was observed in the utilization of and spending on these C1-INH concentrate products nationally. Based on current utilization and accounting for insights from clinical experts, it is anticipated that the utilization of these products will continue to grow at a similar rate unless policy and/or reimbursement changes are made. A difference between the national utilization and total spending was observed, with total spending exhibiting an increased growth rate. The increased growth observed for total spending over time can likely be accounted for by changes in the cost per unit of product over time.

The utilization analysis has differing policy implications related to the growing utilization of these products and their associated costs. From a policy perspective, it would be important to ensure therapies for the management of C1-INH HAE are available to those who need them while, at the same time, ensuring the use of these therapies is optimal both from a clinical and economic perspective. Policies, such as implementing clinical reimbursement criteria that aim to optimize and standardize current utilization, would likely help reduce utilization and spending. In contrast, policies that aim to only reduce costs, such as price negotiations, would only reduce spending and likely not impact utilization. An important note is that the current utilization analysis only incorporates data for two currently accessible C1-INH concentrate products, i.e., Berinert and Cinryze. As more products may become accessible to patients with C1-INH HAE in the future (e.g., Haegarda and lanadelumab), it is unknown, for now, how the utilization would shift in response. However, panellists did suggest the pool of patients potentially seeking LTP may increase over time as new

products intended for SC administration become available, and preference may evolve to favour products with the most convenient dosing regimens.

Variation in the patterns of use across jurisdictions was observed and a geographic trend emerged. Specifically, in the Atlantic provinces, utilization and spending were often above the national average, with higher rates of C1-INH concentrate distribution. Further exploration of current treatment patterns and the influence of key prescribers may drive these trends for a highly specialized treatment. Varying LTP use may drive utilization trends, and the rise in this modality in 2013 may be the driving force for the growing rates of use.[5,39] Evidence of this shift was seen in the user-level analysis, which exhibited a steep climb in the number of units per user in 2014. It should be noted that nearly half of all units distributed were sent to Ontario. If changes were to be made, ensuring their impact in the largest province may serve to be an important strategy.

This analysis is subject to a number of limitations. First, as previously mentioned, the data source only includes aggregate distribution volumes of Berinert and Cinryze without clinical information such as associated indications or patient information (i.e., age, sex). This precluded the ability to conduct an analysis of the appropriateness or changing modalities of use of these products. Future work to better understand current treatment patterns is necessary; access to more detailed data will facilitate such work. Another limitation is the fact that our analysis included only two C1-INH concentrate products, i.e., Berinert and Cinryze. There are other drug products available in Canada for either the treatment of acute C1-INH HAE attacks, i.e., icatibant, or the prevention of these attacks, i.e., lanadelumab. However, as the distribution stream for these products is through jurisdictional drug programs, the CBS data set did not include them. Lastly, it is unknown if the insights from the user-level analysis from British Columbia can be extrapolated to the rest of the country.

Economic Evaluation

LTP improved health outcomes in patients with C1-INH HAE; however, none of the LTP treatments (Cinryze, lanadelumab, or Berinert) were cost-effective at WTP thresholds of $50,000, $100,000, or $150,000 per QALY compared with no LTP. In the base-case sequential analysis, Cinryze was associated with an ICUR of $673,632 compared with no LTP, whereas lanadelumab was associated with an ICUR of $12,992,477 compared with Cinryze. Berinert was dominated by lanadelumab, which means lanadelumab was associated with lower total costs and higher QALYs compared with Berinert. If Haegarda is marketed in Canada at the price provided by CBS, then Haegarda would be dominated by lanadelumab. If Haegarda is marketed at a cost equal to Cinryze, then it would become the lowest-cost option.

As described in the ICER report, the results of the economic model are highly sensitive to clinical inputs, such as baseline rate of acute attacks. In the Canadian context, an attack rate of 9.1 per month would allow Cinryze to reach a cost-effectiveness threshold of $150,000 per QALY; however, even at an attack rate of 10 per month, lanadelumab and Berinert would still not be cost-effective at WTP thresholds of $50,000 and $150,000 per QALY. Furthermore, there is no percentage of patients who can switch to a dosing schedule of every four weeks for lanadelumab that would make this therapy cost-effective at a WTP threshold of $150,000 per QALY, meaning that even if all patients on lanadelumab are put on an every-four-weeks dosing schedule, this therapy would still not be cost-effective at a WTP threshold of $150,000 per QALY.

Since the societal costs of C1-INH HAE are small relative to the total health care costs, a societal-perspective analysis resulted in ICURs similar to the base-case analysis: Cinryze and lanadelumab had ICURs of $533,392 and $12,762,387 per QALY, respectively.

Overall, the analysis suggests that at their current prices, none of the therapies intended for LTP are cost-effective. Even by extending WTP thresholds beyond the standard $50,000 per QALY to include ICERs of $100,000 or $150,000 per QALY, or even higher, these therapies are not economically attractive. It should be noted, however, that in light of the significant uncertainty around key model inputs, results should be interpreted with caution.

Budget Impact Analysis

From a budget impact perspective, the analysis demonstrates that adoption of the new therapies for LTP of C1-INH HAE attacks has the potential to introduce savings for the public payer when considering drug costs alone compared with the current practice considered in our analysis, which is largely based on the use of Berinert for LTP. While acknowledging the potential savings associated with the funding of these new therapies, it should be noted that policies for the funding of LTP with C1-INH concentrate or non-plasma–derived therapies result in higher costs than funding the treatment of HAE attacks (i.e., no LTP). These findings, taken in conjunction with the results from the utilization analysis and cost-utility analysis, indicate that while none of the therapies intended for LTP meet the current standard cost-effectiveness thresholds, their high prices and increasing rate of utilization may significantly impact the capacity of public payers to provide such therapies. Another observation is that, although the use of LTP may reduce the frequency of on-demand treatment, it does not eliminate it. As such, funding of the latter remains important, as access to on-demand therapy is important and can be life-saving in certain situations. Based on these observations and on the prices of products considered in the cost-utility and budget impact analyses, it may be stated that the economic value of therapies intended for the routine prevention of C1-INH HAE attacks is low. In order to improve the economic value of these therapies, significant price reductions are needed. To that extent, conversion to new therapies may also help reduce the budget impact of funding therapies for LTP. As results from the BIA are quite sensitive to the number of patients using the LTP therapies, another option to improve both the economic value and the affordability of these products would be to limit the number of patients who may access these treatments. Within this context, our consultation with the four experts gathered for this project may help in identifying subgroups of patients who may derive a higher level of benefit from LTP compared with the general population of individuals with C1-INH HAE.

Summary

Overall, our findings indicate that access to products for LTP of C1-INH HAE attacks is important for a significant proportion of patients with HAE, as they may derive clinical and functional benefits from these therapies. The utilization of the currently funded C1-INH concentrate products has substantially and steadily increased over time, particularly for Berinert, although the main driver of this growth remains undetermined. Our analysis suggests the utilization of these drugs is expected to continue to rise in future years. While utilization data were available only for Berinert and Cinryze, consultation with clinical experts suggests that the availability of new therapies for the routine prevention of C1-INH HAE attacks may result in more patients electing to use LTP in addition to using on-demand therapy. Over time, patients may switch from plasma-derived LTP therapies to lanadelumab, given the more convenient dosing schedule of the latter. It may be worthwhile to align policies across funding agencies to ensure patients have equal access to medicines.

Of note, part of the limitations of the analyses is the lack of information on the utilization of plasma-derived products, in particular, the number of patients and the reasons for use. Given the anticipated continued rise in the utilization of these products, and the growing availability of non-plasma therapies, there may be an opportunity to align the level of information collected for both plasma-derived and non-plasma–derived products. Access to complete data sets for these products would result in improved understanding of key utilization drivers and potentially improved implementation of funding policies for therapies for LTP of C1-INH HAE attacks in the future. Overall, the analyses conducted in this report suggest that funding decisions regarding LTP of acute attacks need to consider both the clinical and economic values of currently available and future therapies. Although still limited, evidence would suggest that such policies would be most impactful if focused on price reduction and careful selection of patients.

Conclusion

The use of LTP to prevent acute attacks is recognized as an important treatment option for patients with C1-INH HAE, as these treatments have the potential to reduce the frequency of attacks and improve patient health-related quality of life. Patients with frequent and severe attacks, particularly if associated with significant morbidity and reduction in daily function, would be expected to benefit most from LTP therapies. The utilization of these products is sharply increasing in Canada and, at their current prices, none of the therapies intended for LTP are cost-effective. This increased utilization, combined with the high prices of products for LTP of C1-INH HAE attacks, has considerable budgetary implications for public payers. Careful selection of patients and a substantial reduction in the price of these products would be avenues to be considered to ensure the sustainability of access to these therapies in Canada.

References

1. Betschel S, Badiou J, Binkley K, et al. Canadian hereditary angioedema guideline. *Allergy Asthma Clin Immunol.* 2014;10(1):50.
2. Prophylaxis for hereditary angioedema with lanadelumab and C1 inhibitors: effectiveness and value, final evidence report. Boston (MA): Institute for Clinical and Economic Review; 2018: https://icer-review.org/wp-content/uploads/2018/03/ICER_HAE_Final_Evidence_Report_111518.pdf. Accessed 2019 Nov 28.
3. Guidelines for the economic evaluation of health technologies: Canada. 4th ed. Ottawa (ON): CADTH; 2017 Mar: https://www.cadth.ca/dv/guidelines-economic-evaluation-health-technologies-canada-4th-edition. Accessed 2019 Aug 01.
4. Betschel S, Badiou J, Binkley K, et al. The international/Canadian hereditary angioedema guideline. *Allergy Asthma Clin Immunol.* 2019;15(1):72.
5. Henry Li H, Riedl M, Kashkin J. Update on the use of C1-esterase inhibitor replacement therapy in the acute and prophylactic treatment of hereditary angioedema. *Clin Rev Allergy Immunol.* 2019;56(2):207-218.
6. Aygoren-Pursun E, Magerl M, Maetzel A, Maurer M. Epidemiology of bradykinin-mediated angioedema: a systematic investigation of epidemiological studies. *Orphanet J Rare Dis.* 2018;13(1):73.
7. Shire. Health Canada has authorized TAKHZYRO (lanadelumab injection), a first-of-its-kind monoclonal antibody treatment for the prevention of hereditary angioedema (HAE) attacks. 2018; https://www.globenewswire.com/news-release/2018/09/20/1573574/0/en/Health-Canada-has-authorized-TAKHZYRO-TM-lanadelumab-injection-a-first-of-its-kind-monoclonal-antibody-treatment-for-the-prevention-of-hereditary-angioedema-HAE-attacks.html. Accessed 2019 Nov 28.
8. Cotiguala LM, Coover KL, Bewtra AK, Malesker MA. Advances in the pharmacotherapy of hereditary angioedema. *US Pharmacist.* 2015;40(10):HS17-HS21.
9. Berinert 500/1500 (C1 esterase inhibitor, human): powder and diluent for solution for injection, for intravenous administration [product monograph]. Ottawa (ON): CSL Behring Canada, Inc.; 2019 May 31: https://pdf.hres.ca/dpd_pm/00051513.PDF. Accessed 2019 Nov 28.
10. Health Canada. Drug product database product information: Berinert. 2019; https://health-products.canada.ca/dpd-bdpp/index-eng.jsp. Accessed 2019 Nov 28.
11. Health Canada. Drug product database search results summary: Berinert 2019; https://health-products.canada.ca/dpd-bdpp/index-eng.jsp. Accessed 2019 Nov 28.
12. Health Canada. Drug product database product information: Firazyr. 2019; https://health-products.canada.ca/dpd-bdpp/index-eng.jsp. Accessed 2019 Nov 28.
13. Firazyr (icatibant injection): solution, 30 mg / 3 mL (10 mg / mL) as icatibant acetate single-use prefilled syringe, subcutaneous [product monograph]. Lexingtron (MA): Shire Orphan Therapies, LLC.; 2019 June 26: https://pdf.hres.ca/dpd_pm/00051974.PDF. Accessed 2019 Nov 28.
14. Health Canada. Drug product database product information: Cinryze. https://health-products.canada.ca/dpd-bdpp/index-eng.jsp. Accessed 2019 Nov 28.
15. Cinryze (C1 inhibitor [human]): 500 IU lyophilized powder/vial, reconstituted with 5 mL of diluent C1 inhibitor [product monograph]. Lexington (MA): ViroPharma Biologics Inc.; 2015 Aug 13: https://pdf.hres.ca/dpd_pm/00031617.PDF. Accessed 2019 Nov 28.
16. Health Canada. Drug product database product information: Haegarda. 2019; https://health-products.canada.ca/dpd-bdpp/index-eng.jsp. Accessed 2019 Nov 28.
17. Health Canada. Drug product database search results summary: Haegarda. 2019; https://health-products.canada.ca/dpd-bdpp/index-eng.jsp. Accessed 2019 Nov 28.
18. Haegarda C1 esterase inhibitor subcutaneous (human) powder and diluent for solution for injection, for subcutaneous administration [product monograph]. Ottawa (ON): CSL Behring Canada Inc.; 2019 Aug 13: https://pdf.hres.ca/dpd_pm/00052648.PDF. Accessed 2019 Nov 28.
19. Health Canada. Drug product database search results summary: Takhzyro. 2019; https://health-products.canada.ca/dpd-bdpp/index-eng.jsp. Accessed 2019 Nov 28.
20. Takhzyro (lanadelumab): 150 mg/mL solution for subcutaneous injection [product monograph]. Toronto (ON): Shire Pharma Canada ULC; 2018 Sep 19: https://pdf.hres.ca/dpd_pm/00047437.PDF. Accessed 2019 Nov 28.
21. BloodBrief: an update on C1 inhibitor concentrate. Ottawa (ON): Canadian Blood Services; 2017: https://blood.ca/sites/default/files/BloodBrief-C1-inhibitor-Overview-Nov2017.pdf. Accessed 2019 Nov 28.
22. Statistics Canada. Population estimates on July 1st, by age and sex. 2019; https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1710000501. Accessed 2019 09 30.
23. Carlson JJ, Lubinga S. The University of Washington CHOICE Institute hereditary angioedema cost-effectiveness model.
24. Banerji A, Riedl M, Bernstein J, et al. OR034 Lanadelumab for prevention of attacks in hereditary angioedema: results from the phase 3 HELP study. *Ann Allergy Asthma Immunol.* 2017;119(5):S5.
25. Longhurst H, Cicardi M, Craig T, et al. Prevention of hereditary angioedema attacks with a subcutaneous C1 inhibitor. *N Engl J Med.* 2017;376(12):1131-1140.

26. Zuraw BL, Busse PJ, White M, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *N Engl J Med.* 2010;363(6):513-522.

27. Nordenfelt P, Dawson S, Wahlgren CF, Lindfors A, Mallbris L, Bjorkander J. Quantifying the burden of disease and perceived health state in patients with hereditary angioedema in Sweden. *Allergy Asthma Proc.* 2014;35(2):185-190.

28. Cicardi M, Agostoni A. Hereditary angioedema. *N Engl J Med.* 1996;334(25):1666-1667.

29. Nzeako UC, Frigas E, Tremaine WJ. Hereditary angioedema: a broad review for clinicians. *Arch Intern Med.* 2001;161(20):2417-2429.

30. Maurer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-the 2017 revision and update. *Allergy.* 2018;73(8):1575-1596.

31. Mendivil J, DerSarkissian M, Chang R, et al. Real-world treatment patterns and clinical outcomes among patients with hereditary angioedema (HAE) in Canada. *Canadian Society of Allergy and Clinical Immunology (CSACI) Annual Scientific Meeting.* 2019 Oct 23-27.

32. Bank of Canada. Daily exchange rates lookup. 2019; https://www.bankofcanada.ca/rates/exchange/daily-exchange-rates-lookup/?series%5B%5D=FXUSDCAD&lookupPage=lookup_daily_exchange_rates_2017.php&startRange=2009-11-04&rangeType=range&rangeValue=&dFrom=2018-01-01&dTo=2018-12-31&submit_button=Submit. Accessed 2019 Sep 26.

33. BC PharmaCare. Drug information: lanadelumab. Victoria (BC): Ministry of Health; 2019: https://www2.gov.bc.ca/assets/gov/health/health-drug-coverage/pharmacare/your-voice-drug-info/lanadelumab_takhzyro_3660_dis.pdf. Accessed 2019 Nov 28.

34. DeltaPA. Ottawa (ON): IQVIA; 2019: https://www.iqvia.com/. Accessed 2019 Aug 22.

35. Specialised Commissioning Team. Clinical commissioning policy: plasma-derived C1-esterase inhibitor for prophylactic treatment of hereditary angioedema (HAE) types I and II. London (GB): NHS England; 2016: https://www.england.nhs.uk/wp-content/uploads/2018/07/Plasma-derived-C1-esterase-inhibitor-for-prophylactic-treatment-of-hereditary-angioesema-types-I-and-II.pdf. Accessed 2019 Nov 28.

36. Medical Services Advisory Committee. Public summary document: application no. 1394 – C1 esterase inhibitor concentrate for hereditary angioedema. Canberra (AU): Department of Health; 2015: http://www.msac.gov.au/internet/msac/publishing.nsf/Content/DC572CB3CD42BD2FCA25801000123BFE/$File/1394-FinalPSD-C1%20Esterase.pdf. Accessed 2019 Nov 28.

37. Wilson DA, Bork K, Shea EP, Rentz AM, Blaustein MB, Pullman WE. Economic costs associated with acute attacks and long-term management of hereditary angioedema. *Ann Allergy Asthma Immunol.* 2010;104(4):314-320.

38. CADTH Canadian Drug Expert Committee (CDEC) final recommendation: takhzyro (Shire Pharma Canada ULC). Ottawa (ON): CADTH; 2019: https://cadth.ca/sites/default/files/cdr/complete/SR0618%20Takhzyro%20-%20CDEC%20Final%20Recommendation%20November%2022%2C%202019_for%20posting.pdf. Accessed 2019 Nov 25.

39. Riedl MA, Banerji A, Manning ME, et al. Treatment patterns and healthcare resource utilization among patients with hereditary angioedema in the United States. *Orphanet J Rare Dis.* 2018;13(1):180.

40. National Institute for Health and Care Excellence. Final appraisal document: lanadelumab for preventing recurrent attacks of hereditary angioedema. 2019; https://www.nice.org.uk/guidance/ta606/documents/final-appraisal-determination-document-2. Accessed 2019 Nov 28.

41. Aetna. Hereditary angioedema. 2019; http://www.aetna.com/cpb/medical/data/700_799/0782.html. Accessed 2019 Nov 28.

42. Clinical criteria: hereditary angioedema agents. Indianapolis (IN): Anthem; 2019: https://www11.anthem.com/provider/noapplication/f0/s0/t0/pw_g357970.pdf. Accessed 2019 Nov 28.

43. C1 esterase inhibitor (Haegarda). *Injections: drugs a-d policy*. Sacramento (CA): California Department of Health Care Services; 2019.

44. Cigna drug and biologic coverage policy: hereditary angioedema (HAE) therapy. Bloomfield (CT): Cigna; 2018: https://cignaforhcp.cigna.com/public/content/pdf/coveragePolicies/pharmacy/ph_1019_coveragepositioncriteria_hereditary_angioedema.pdf. Accessed 2019 Nov 28.

45. Clinical policy: C1 esterase inhibitors (berinert, cinryze, haegarda, ruconest). St Louis (MO): Centene Corporation; 2018: https://ambetter.arhealthwellness.com/content/dam/centene/ar-health-wellness/policies/Ambetter/Ambetter_Pharmacy_Policy/AR.PHAR.202%20C1%20Esterase%20Inhibitors%20(Berinert%2C%20Cinryze%2C%20Haegarda%2C%20Ruconest)%2012.01.17.pdf. Accessed 2019 Nov 28.

46. Pharmacy / medical policy – 5.01.587: hereditary angioedema. Mountlake Terrace (WA): Premera Blue Cross; 2019: https://www.premera.com/medicalpolicies/5.01.587.pdf. Accessed 2019 Nov 28.

47. Fryar C, ., Gu Q, Ogden C, Flegal K. Anthropometric reference data for children and adults; United States, 2011-2014. *National Center for Health Statistics* Hyattsville (MD) 2016: https://stacks.cdc.gov/view/cdc/40572. Accessed 2019 Nov 28.

48. Riedl MA, Bygum A, Lumry W, et al. Safety and usage of C1-inhibitor in hereditary angioedema: berinert registry data. *J Allergy Clin Immunol Pract* 2016;4(5):963-971.

49. Riedl M, Gower RG, Chrvala CA. Current medical management of hereditary angioedema: results from a large survey of US physicians. *Ann Allergy Asthma Immunol.* 2011;106(4):316-322.e314.

50. Zanichelli A, Arcoleo F, Barca MP, et al. A nationwide survey of hereditary angioedema due to C1 inhibitor deficiency in Italy. *Orphanet J Rare Dis.* 2015;10:11.

51. Lumry W, Bernstein J, Cicardi M, et al. P153 Subcutaneous c1 inhibitor prophylaxis substantially reduces the need for rescue medications in the compact study. *Ann Allergy Asthma Immunol.* 2017;119(5):S39.

52. Zanichelli A, Mansi M, Azin GM, et al. Efficacy of on-demand treatment in reducing morbidity in patients with hereditary angioedema due to C1 inhibitor deficiency. *Allergy.* 2015;70(12):1553-1558.

53. Zilberberg MD, Nathanson BH, Jacobsen T, Tillotson G. Descriptive epidemiology of hereditary angioedema emergency department visits in the United States, 2006-2007. *Allergy Asthma Proc.* 2011;32(5):390-394.

54. Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to CI-INH deficiency. *J Allergy Clin Immunol.* 2012;130(3):692-697.

55. Zuraw B. Hereditary angioedema: treatment of acute attacks. In: Sainj S, ed. *UpToDate*. Waltham (MD): UpToDate; 2018: www.uptodate.com. Accessed 2019 Nov 28.

56. Federici C, Perego F, Borsoi L, et al. Costs and effects of on-demand treatment of hereditary angioedema in Italy: a prospective cohort study of 167 patients. *BMJ Open.* 2018;8(7):e022291.

57. Highlights of collective agreement changes as a result of the kaplan award and items in agreement between ONA and participating hospitals. Toronto (ON): Ontario Nurses' Association; 2018: https://www.ona.org/wp-content/uploads/ona_hospitalcahighlightdoc_20180731f.pdf. Accessed 2019 Sep 27.

Appendix 1: Summary of Clinical Panel Consultation

Current Treatments for Hereditary Angioedema and Canadian Clinical Practice

1.1 The 2014 Canadian hereditary angioedema (HAE) guideline quotes a prevalence estimate for HAE of 1:50,000. Is this the best existing estimate for the Canadian population, or are there other estimates that may be more accurate?

The 1:50,000 estimate is generally accepted and is the most widely used. It is possible that prevalence is higher is some regions than in others, since it is an autosomal dominant condition. The panel is not aware of any other estimates that are used for the Canadian population.

1.2 In current practice, when is long-term prophylaxis (LTP) for prevention of attacks considered for a patient with HAE?

What factors influence the decision of whether to initiate LTP?

Based on your clinical experience, please estimate (if possible) the proportion of Canadian patients with HAE receiving:

a) C1-esterase inhibitor (C1-INH) for on-demand treatment
b) Oral LTP
c) C1-INH or lanadelumab LTP

LTP is considered for patients who need to control frequent and/or severe HAE attacks. Aside from frequency and severity of attacks, impact on patients in terms of health-related quality of life must also be taken into consideration. Attacks can lead to patients missing days at work or school and experiencing disability, especially if not treated. The goal of LTP for HAE is to allow patients to live a normal life and work, go to school, perform daily activities, and participate in recreational and social activities. Patients may avoid certain activities that can trigger their attacks, such as strenuous exercise or working a night shift, unless they are on prophylaxis.

Based on clinical experience, it is estimated that 50% to 70% of patients with HAE are receiving LTP. Most patients on LTP are receiving C1-INH and the proportion of patients on oral LTP will likely decrease over time. However, some patients prefer to stay on oral LTP rather than switch to C1-INH LTP. Lanadelumab is currently available through exceptional access only.

Based on the results from a retrospective study of 51 Canadian patients with HAE type 1 or type 2 at four different centres:[31]

- 65% of patients were receiving LTP
- before 2014, 76% of those on LTP were using androgens for LTP
- after 2014, of those receiving LTP, 82% were using C1-INH (for LTP), 18% were using androgens, and 6% were using antifibrinolytics
- a small number of patients receive lanadelumab through exceptional access programs, but these patients were not captured in the study
- 92% of patients with HAE received on-demand treatment
- the mean annual attack rate after 2014 was 16.1 attacks in those not using LTP (based on eight patients) versus and 10.7 attacks in those on LTP (based on 16 patients)

1.3 Please describe what factors you would consider in choosing between oral LTP, C1-INH LTP, and lanadelumab LTP when initiating LTP in a patient with HAE.

How might a patient progress on therapy over time if management of their HAE attacks is not optimal?

Most patients will start with on-demand treatment alone, either with icatibant or C1-INH. Patients starting on C1-INH are given two treatments for this purpose. If patients have more frequent attacks, they may gradually transition to using C1-INH twice weekly, which would be considered LTP.

Oral prophylaxis consists of androgens (e.g., danazol) or tranexamic acid. Tranexamic acid has gastrointestinal side effects and is not very effective in preventing attacks. Long-term use of danazol is associated with adverse effects, including masculinizing effects and risk of hepatocellular carcinoma. Pediatric patients requiring LTP receive C1-INH, since they cannot use androgens. Most patients with HAE start experiencing attacks at around the age of 12 years.

Patients with HAE who are pregnant would not receive lanadelumab, as there is little experience with using it during pregnancy. Treatment with C1-INH is safe during pregnancy, but androgens cannot be used and are discontinued upon pregnancy or when planning for pregnancy.

Patients who are taking danazol as LTP may be weaned from danazol and switched to intravenous (IV) or subcutaneous (SC) C1-INH if danazol is not effective at a dose of up to 200 mg/day or if they experience many adverse effects. Women tend to switch from danazol more often than men due to the adverse effects. Danazol may lose efficacy in men who become obese and have increased circulating estrogen. Due to the adverse effects associated with long-term danazol use, it is not suitable for patients unless it is the patient's preferred treatment and unless they agree to long-term monitoring.

The route of administration also plays a role in the adoption of LTP. The IV and SC administration routes may act as a deterrent to some patients in terms of using C1-INH or lanadelumab. Some patients choose to solely use on-demand treatment with icatibant or not treat their attacks rather than go on LTP with C1-INH due to the mode of administration. Port-a-caths are generally not used to facilitate IV access, as they can lead to thrombosis and infection. Based on clinical experience, patients who are willing to be trained in IV administration are able to do so successfully. Patients who are significantly impacted by their attacks are motivated to use IV therapy. SC administration, either twice a week with C1-INH or every two weeks with lanadelumab, is more feasible for patients than IV administration twice a week. Some clinicians currently treating patients with HAE may not be aware of, or may not be comfortable with, the use of SC C1-INH (as this is beyond the Health Canada–approved indications for currently available C1-INH products) and their patients may not initiate LTP with C1-INH despite frequent attacks if they are not able to receive IV C1-INH.

Coverage of therapies and availability of access (e.g., a patient may live far away from a blood bank) can also have an impact on the therapies patients receive.

Optimal Use of C1-Esterase Inhibitors and Lanadelumab in Hereditary Angioedema

1.4 Which patients with HAE are most likely to benefit from LTP with C1-INH or lanadelumab? Please estimate (if possible) the proportion of patients with HAE that this would represent.

As previously discussed, patients who would benefit from LTP are those with frequent and/or severe attacks who are impacted in terms of quality of life and social functioning. Some patients are unable to treat their attacks acutely due to lack of access, lack of response with icatibant, or inability to self-administer on-demand IV C1-INH treatment. These patients may also benefit from SC LTP with C1-INH or lanadelumab. Patients who require frequent hospitalization or use of the emergency department due to attacks should be considered for LTP.

Currently, it is difficult to predict the degree of benefit to patients in response to LTP initiation. There is not necessarily a relationship between baseline attack characteristics (i.e., frequency and severity) and response to LTP; for example, patients with very different baseline attack frequencies may end up with a similar attack frequency after initiating LTP. Effectively, these patients would have different relative reductions in attack frequency, but there is no way to predict this. While clinical trial results for LTP with SC C1-INH have shown that the higher dosage is effective in reducing attacks, it is harder to predict who might benefit in the real world. The patient population in the clinical trial for LTP with SC C1-INH was likely skewed toward a more symptomatic population. Further, adherence to the recommended dosage in the real-world setting may differ from that of a clinical trial. One notable outcome in the SC C1-INH clinical trial was that laryngeal attacks were eliminated in the higher-dosage group.

There is no way to predict if patients would see more benefit from one type of treatment (C1-INH or lanadelumab) over another.

At least 50% of patients with HAE would benefit from LTP and, potentially, almost all patients would experience a reduction in the number of attacks. In addition, there are some patients not currently on LTP by choice (e.g., due to the need for injections for LTP with C1-INH) who would likely benefit from LTP.

1.5 How can clinicians identify the patients most likely to benefit from C1-INH or lanadelumab for LTP?

As a starting point for discussion, we have compiled the following treatment-initiation criteria regarding C1-INH and/or lanadelumab for LTP (from the National Health Service [NHS] England Clinical Commissioning Policy and US health insurance policies; see the "Summary of C1-INH and lanadelumab coverage" document for details.) [Note: this document is included in Appendix 3 of the report.]

- **a) Age (≥ 6 years old or ≥ 12 years old)**
- **b) Confirmed diagnosis (based on C1-INH antigenic level, C1-INH functional level, and/or C4 level)**
- **c) Frequency of attacks (≥ 1 or 2 attacks per month, or ≥ 2 attacks per week)**
- **d) Severity of attacks (moderate or severe, severe, or clinically significant[a])**
- **e) Has tried (and failed or is intolerant to) or has a contraindication to other agents for LTP of HAE (androgens or antifibrinolytics)**
- **f) Medications known to cause angioedema have been evaluated and discontinued, when appropriate**

For each item, please comment on the appropriateness of implementing a similar criterion to identify Canadian patients who are the most likely to benefit from LTP with C1-INH or lanadelumab.

[a] From the NHS England Clinical Commissioning Policy: *"A clinically significant attack is one which is i) potentially life threatening because it affects the head or neck or ii) causes pain or disability such that the patient cannot continue their normal activities. This may be due to disabling cutaneous swelling, sufficient to prevent the patient from undertaking normal activities or severe abdominal pain which will not respond to oral analgesia. Varying treatment pathways do not imply that an attack requiring hospital treatment is necessarily more significant than one which can be treated with self-administered therapies."*

1.5 How can clinicians identify the patients most likely to benefit from C1-INH or lanadelumab for LTP? (Continued)

a) Age is considered in the context of the approved indications for C1-INH products and lanadelumab. However, clinicians may deviate from approved indications if there are no other options or if clinical guidelines recommend this.

b) A confirmed diagnosis of type 1 or 2 HAE is important for initiating LTP and this diagnosis is standardized across Canada. Diagnosis should be based on the presence of low C1-INH functional level and/or low C1-INH antigenic level. A low C4 level should not be required, as C4 level may be normal in patients with type 1 or 2 HAE. Patients with type 3 HAE (normal C1-INH) may be considered for C1-INH LTP, though there is insufficient evidence to support a recommendation for or against this practice.

c and d) There is agreement that there should not be a cut-off in terms of frequency or severity of HAE attacks for determining whether a patient should receive LTP with C1-INH or lanadelumab. Both frequency and severity of attacks need to be considered, in addition to impact on health-related quality of life and being able to live a normal life. For example, a frequency as low as one attack per month has significant impact if the attack requires hospitalization (as is the case for laryngeal attacks) and keeps the patient from work for several days. All of these factors need to be considered together, along with patient safety, and it would be impossible to set hard limits that could apply to all patients. Assessment of attack severity can be difficult, as early on-demand treatment of an attack can prevent or greatly mitigate symptoms and it would be inappropriate to ask a patient to refrain from treating an attack in order to determine its severity. The examples of criteria from other jurisdictions are problematic and not aligned with clinical practice. The NHS criteria around frequency and severity of attacks ("*two or more clinically significant attacks per week, despite oral prophylaxis*") mean that a patient would have to be very symptomatic before initiating LTP with C1-INH. Also, the part of the NHS definition of "clinically significant attack" referring to severe abdominal pain which will not respond to oral analgesia is outdated, as these attacks should be treated with an HAE therapy and any analgesia would be adjunctive. The Australian recommendation of eight attacks per month as a threshold would mean that such a patient would already be using on-demand therapy twice a week and would effectively be on LTP (with their attacks not being appropriately controlled).

e) As per clinical guidelines, there is agreement among clinicians that patients should not have to try and fail on oral LTP before starting C1-INH or lanadelumab LTP. In addition to the considerations already discussed regarding oral LTP, danazol is not indicated for the treatment of HAE and there is a shortage of danazol in Canada. Antifibrinolytics are not well tolerated and are not effective. The 2014 Canadian guideline specifies that patients do not need to fail other LTP therapies before LTP with C1-INH is considered.

f) Medications known to cause angioedema would be eliminated as part of the standard management of patients with HAE. Patients with HAE would not be placed on medications that exacerbate angioedema.

1.6 Which patients would be least suitable for LTP with C1-INH or lanadelumab (and why)?

Asymptomatic patients and patients with mild and/or infrequent attacks would be least suitable for LTP with C1-INH or lanadelumab. Short-term prophylaxis with C1-INH can be used in such patients if they are undergoing surgery or in other situations known to trigger HAE attacks. LTP with C1-INH or lanadelumab is not suitable for patients who are unwilling to perform the injections or lack the means to have them administered. Patients with an unclear diagnosis would also not be suitable. It is not known if patients with type 2 HAE would benefit from C1-INH or lanadelumab LTP and their suitability is currently unclear. Some patients with type 3 HAE have responded to C1-INH treatment. Lanadelumab would not be used in patients under 12 years old (except in cases where there is no other option) or in patients who are pregnant. It was also noted that there will always be some patients who are nonadherent to their therapies, though nonadherence to one therapy does not render a patient unsuitable for a different therapy.

1.7 What outcomes are used to determine whether a patient is responding to LTP with C1-INH or lanadelumab in clinical practice?

For each outcome, please describe how it can be assessed and what would be considered a clinically meaningful response.

Response would be determined by a reduction in the frequency or severity of symptoms, as well as improvement in quality of life and ability to perform activities of daily living. While attack frequency can be measured, the clinical significance of a reduction in attack frequency must be interpreted in the context of other factors, particularly attack severity and use of rescue medication (on-demand treatment). A reduction in attack frequency and/or severity should be accompanied by a reduction in the use of rescue medication, though there may be instances in which a reduction in attack frequency and/or severity is clinically meaningful despite no change in the use of rescue medication.

Being able to return to a normal life is important for patients. Patients may be differentially impacted by a reduction in attacks based on what their normal work or school life and activities were prior to the onset of HAE; therefore, it is difficult to assess or measure response in terms of ability to perform activities of daily living, since patients tend to modify their activities in response to their disability. A reduction in visits to the emergency department or hospitalizations would also be relevant, though such outcomes are not typically assessed in clinical trials.

Assessing response to therapy generally involves having a discussion with the patient. Recent attack frequency or severity are typically assessed in clinical practice by simply asking the patient. In clinical trials, patients recorded attack onset, duration, severity, and resolution in a diary. Since frequency of attacks can vary in the short term, attack frequency should be assessed by evaluating HAE attacks that occur over a period of at least one month.

1.8 How long after treatment initiation would you assess a patient's response to LTP with C1-INH or lanadelumab? How often would you continue to monitor the patient's response?

A follow-up period of three to six months after treatment initiation would be reasonable and would align with how often clinicians currently see their patients with HAE. However, it may be more likely for clinicians to see their patients every six months.

1.9 Would dosage adjustments be considered for C1-INH or lanadelumab (e.g., if patients have been attack-free for a certain period of time)?

If a patient's attacks are not well controlled on the starting dosage regimen for C1-INH, dose or frequency of dosing can be increased. There has been experience with dosages of IV C1-INH of up to 3,000 IU every four days, and dosages of SC C1-INH of up to 60 IU/kg twice a week for LTP. Patients who continue to experience attacks on SC C1-INH LTP may be switched to IV C1-INH LTP to facilitate the administration of larger volumes. If improvements are not seen with these adjustments, options include switching to lanadelumab (if available) or add-on therapy with low-dose androgen for patients on a maximum dose of C1-INH. Combination therapy with C1-INH LTP and lanadelumab LTP would generally not be considered, given the clinical trial results for lanadelumab and availability of effective therapies for on-demand treatment. It is estimated that the combination of C1-INH LTP and lanadelumab LTP would be used in less than 5% to 10% of patients with HAE. Patients would most likely switch to C1-INH LTP if lanadelumab was not effective.

If a patient is attack-free for six to 12 months on a stable regimen, then a dose reduction or reduction in dose frequency can be considered for C1-INH and, potentially, lanadelumab.

1.10 **Would you consider discontinuing LTP with C1-INH or lanadelumab in any patients and, if so, what factors should be considered for this decision?**

It is possible for some patients to go into remission and, potentially, these patients could discontinue LTP. This may be more likely in patients who have acquired angioedema; for example, LTP for HAE may be discontinued following treatment of the underlying malignancy. Patients may titrate downward, and trial discontinuation can be considered for a stable patient who has access to on-demand treatment. However, based on clinical experience, it is rare to completely discontinue LTP, even in a stable patient, due to lack of experience with discontinuation and the potential consequences if the patient does not remain stable. Lanadelumab would be discontinued for patients who become pregnant.

1.11 Which type(s) of specialist would be required to diagnose, treat, and monitor patients who might receive LTP with C1-INH or lanadelumab? Is there an existing specialist network (or would it be feasible to create such a network) for determining individual patient suitability for LTP with C1-INH or lanadelumab?
Patients with HAE are diagnosed, treated, and monitored by hematologists or clinical immunologists/allergists. Hospital privileges and access to a blood bank are required to be able to prescribe C1-INH. There is the Canadian Hereditary Angioedema Network (CHAEN), which is a network of physicians who treat HAE. CHAEN would be positioned to assess or issue recommendations or to review indications, but not to assess individual prescriptions.

Additional Questions

1.12 If either lanadelumab or Haegarda became more accessible to Canadian patients with HAE: a) Would there be a change in the proportion of patients with HAE receiving LTP? b) Would the mix of agents used for LTP change?
Berinert 1500 given subcutaneously at higher doses is identical to Haegarda in terms of C1-INH dosage and route of administration. If Haegarda became available or if lanadelumab became more accessible, the proportion of patients receiving LTP would increase, though it is difficult to predict the amount of increase. The ability to market SC C1-INH would likely increase its use. If lanadelumab were more accessible, its use would likely increase and the proportion of patients using C1-INH for LTP would therefore likely decrease. Patients may favour the convenience of biweekly dosing with lanadelumab.

Additional Information

1.13 Is there any additional information you feel is pertinent to the panel discussion?
Due to dependency on plasma and the risk of shortages of these products, it is very important to have choice and flexibility in available therapies for HAE. Further, some patients may be concerned about the perceived risk of infectious agent transmission with blood products.

Appendix 2: Summary of Guidance on Long-Term Prophylaxis From Clinical HAE Guidelines

The background document supplied to the clinical panel members ahead of the panel meeting contained a summary of the 2014 Canadian Hereditary Angioedema (HAE) Guideline.[1] This appendix has been updated with information from the 2019 International/Canadian Hereditary Angioedema Guideline,[4] which was published following the panel meeting.

Table 20: Summary of Clinical Hereditary Angioedema Guidelines

	2019 International/Canadian Guideline[4]	2017 WAO/EAACI Guideline[30]
Use of LTP	Recommendation: *"Long-term prophylaxis may be appropriate for some patients to reduce frequency, duration, and severity of attacks"* (p. 14). LOE: High (96.67% agreement) SOR: Strong (96.67% agreement) Background: "*The aim of LTP is to reduce the frequency and/or severity of attacks of HAE and minimize the impact of HAE on QoL, thereby enabling patients to live normal lives. Some patients may be candidates for long-term therapy, and the benefits and risks associated with such treatments should be explored to optimize patient care"* (pp. 14–15).	*"We recommend that patients are evaluated for long-term prophylaxis at every visit. Disease burden and patient preference should be taken into consideration"* (p. 1583). GOE: D (adapted from existing consensus document) SOR: Strong (100% agreement) Background: *"Long-term prophylaxis should be individualized and considered in all severely symptomatic HAE-1/2 patients taking into consideration the activity of the disease, frequency of attacks, patient's quality of life, availability of healthcare resources, and failure to achieve adequate control by appropriate on-demand therapy"* (p. 1583).
C1-INH for LTP	Recommendation: *"pdC1-INH is an effective therapy for long-term prophylaxis in patients with HAE-1/2"* (p. 15). LOE: High (100% agreement) SOR: Strong (100% agreement) Background: *"Controlled clinical trials have demonstrated that both IV and SC pdC1-INH used for prophylaxis in HAE-1/2 reduces the number, duration, and severity of attacks of angioedema. C1-inhibitor prophylaxis has traditionally been given intravenously. More recent trials have shown higher levels of efficacy when C1-inhibitor is given as a higher dose subcutaneously. The subcutaneous route also reduces the inconvenience and medicalization associated with the intravenous route, and avoids hazards of repeated venipuncture and indwelling catheter, further improving QoL. However, direct comparison between the IV and SC routes has not been subject to formal trial"* (p. 15).	*"We recommend use of C1-inhibitor for first-line long-term prophylaxis"* (p. 1584). GOE: A (high-quality RCT) SOR: Strong (50% to 75% agreement) Background: *"Plasma-derived C1-INH is currently the preferred long-term prophylaxis for the prevention of HAE attacks. (…) Routine prophylaxis with pdC1-INH has been shown to be safe and effective, and it improves quality of life in patients with relatively frequent HAE attacks compared with acute treatment of individual HAE attacks"* (pp. 1583–1584).

	2019 International/Canadian Guideline[4]	2017 WAO/EAACI Guideline[30]
Lanadelumab for LTP	Recommendation: *"Lanadelumab is an effective therapy for long-term prophylaxis in patients with HAE-1/2"* (p. 15). LOE: High (95% agreement) SOR: Strong (92.5% agreement) Background: *"Lanadelumab is a subcutaneously injectable, fully humanized, anti-active plasma kallikrein monoclonal antibody (IgG1/k-light chain). It is administered as 300 mg every 2 weeks, however a dosing interval of 300 mg every 4 weeks may be considered if a patient is well controlled (e.g., attack free) for more than 6 months"* (p. 15).	Not applicable.
Androgens for LTP	Recommendation: *"Attenuated androgens are an effective therapy for long-term prophylaxis in some patients"* (p. 15). LOE: Moderate (90.32% agreement) SOR: Strong (90.32% agreement) Background: *"Although androgens and antifibrinolytics are not recommended as first line, these agents may be considered for LTP in those patients who have already obtained benefit from their use or who have difficulty obtaining first-line options"* (p. 15).	*"We suggest to use androgens as second-line long-term prophylaxis"* (p. 1584). GOE: C (comparative trial with severe methodological limitations or large retrospective observational studies) SOR: Weak (50% to 75% agreement) Background: *"Androgen derivatives have been demonstrated to be effective in HAE-1/2, and the oral administration facilitates their use. However, androgens must be regarded critically, especially in light of their adverse androgenic and anabolic effects, drug interactions, and contraindications. Side effects are numerous and involve the majority of patients; in other words, the absence of side effects is exceptional"* (p.1584).
Antifibrinolytics for LTP	See recommendations on treatment sequencing.	*"Antifibrinolytics are not recommended for long-term prophylaxis. Data for their efficacy are largely lacking, but some patients may find them helpful. They are primarily used when C1-INH concentrate is not available and androgens are contraindicated. Side effects are usually minor"* (p. 1584).
Treatment sequencing	Recommendation: *"Subcutaneous C1-INH or lanadelumab should be used as first-line for long-term prophylaxis"* (p. 15). LOE: Consensus (90% agreement) SOR: Strong (97.37% agreement) Background: *"Although there have not been any head-to-head comparisons of long-term prophylactic agents, hence a consensus level of evidence for efficacy, we strongly agreed that either subcutaneous pdC1-INH or lanadelumab are appropriate as first-line LTP"* (p. 15). Recommendation: *"Attenuated androgens and antifibrinolytics should not be used as first-line prophylaxis in patients with HAE-1/2"* (p. 15). LOE: Consensus (89.47% agreement)	See preceding re: C1-INH for long-term prophylaxis.

	2019 International/Canadian Guideline[4]	2017 WAO/EAACI Guideline[30]
	SOR: Strong (88.89% agreement) Background: *"Androgens can affect serum lipid levels, can be hepatotoxic resulting in hepatitis, and have been associated with hepatocellular adenoma and, in very rare cases, carcinoma. (…) Virilising effects of androgen therapy can occur and include menstrual irregularities, masculinization, irreversible voice alteration, and hirsutism. Psychological side effects include emotional irritability and lability, aggressive behaviour and depression. Androgens interact with several medications. (…) Patients need to be made aware of these side effects when considering and while on androgen therapy, and physicians should carefully consider the risks and benefits for the particular patient. There is a moderate level of evidence showing the benefit of the antifibrinolytic agent tranexamic acid as an LTP agent. (…) These data suggested that antifibrinolytic agents could be useful for LTP for HAE-1/2. However, their role in current LTP was felt to be justified only in certain patient groups due to lack of efficacy and the potential side effects at the dosage studied"* (p. 16).	
Treatment adjustments	Recommendation: *"The decision to start or stop long-term prophylaxis depends on multiple factors and should be made by the patient and an HAE specialist"* (p. 18). LOE: Consensus (97.06% agreement) SOR: Strong (97.06% agreement) Background: *"Reducing or stopping LTP could be considered if the patient has been stable with no evidence of breakthrough attacks of angioedema for a protracted period of time, though no specific guidance can be provided on a specific duration of symptom control and the decision must involve the patient. (…) The patient needs to be informed of the risks and benefits of all therapies, as discussed in the relevant sections above, to enable making an informed decision"* (p. 19).	*"We suggest adaptation of long-term prophylaxis in terms of dosage and/or treatment interval as needed to minimize burden of disease"* (p. 1584). GOE: D (adapted from existing consensus document) SOR: Weak (100% agreement)
Treatment self-administration (by patient or caregiver)	Recommendation: *"All patients should be trained on self-administration of HAE-specific therapies if they are suitable candidates. If patients cannot self-administer therapy, provisions should be made to ensure timely access to all appropriate therapies"* (p. 18). LOE: Low (97.14% agreement) SOR: Strong (100% agreement) Background: *"Geographic and regional disparities in care are known to exist, and self-administration of therapy will remove these. Although, intravenous pdC1-INH requires special considerations including product tracking and patient training, the use of blood products for self-administration is not unique. Hemophilia self-administration programs, which are similar, have been widely implemented and have been shown to be effective. (…) Recent licensing of subcutaneously administered therapies will further simplify self-administration"* (p. 18).	*"We recommend that all patients who are provided with on-demand treatment licensed for self-administration should be taught to self-administer"* (p. 1588). GOE: C (comparative trial with severe methodological limitations or large retrospective observational studies) SOR: Strong (100% agreement) Background: *"Self-administration is crucial for an effective on-demand therapy as early treatment in the course of an attack has been shown to be more effective and may prevent complications. (…) Similarly, self-administration facilitates long-term prophylaxis"* (p. 1588).

	2019 International/Canadian Guideline[4]	2017 WAO/EAACI Guideline[30]
Quality of life	Recommendation: *"Health care providers should routinely assess quality of life in HAE patients using validated instruments in order to optimize HAE management"* (p. 20). LOE: Consensus (97.37% agreement) SOR: Strong (94.8% agreement) Background: *"Assessment of HAE control as it relates to the frequency, duration, and severity of attacks is not the only thing to consider when monitoring patients. Data suggests that factors which relate to a patient's QoL are important when following patients with HAE. (…) Validated instruments that are short, specific, and responsive are needed to routinely assess HAE patients and optimize their management"* (p. 20).	See recommendations on C1-INH for LTP.
LTP during pregnancy and lactation	Recommendation: *"When long-term prophylaxis is indicated in pregnancy, pdC1-INH is the treatment of choice"* (p. 16). LOE: Consensus (97.3% agreement) SOR: Strong (97.37% agreement) Background: *"The data from observational studies and retrospective reviews demonstrated that pdC1-INH was generally safe and not associated with any neonatal abnormalities or treatment-related adverse events during the study periods. Although the data were not of high quality, we strongly recommended pdC1-INH when LTP is required in pregnancy"* (p. 16). Recommendation: *"Attenuated androgens should not be used during pregnancy or during the breastfeeding period"* (p. 16). LOE: Consensus (100% agreement) SOR: Strong (100% agreement) Background: *"Androgens are contraindicated during pregnancy as these drugs can have significant effects on the normal development of the fetus, including masculinization"* (p. 16).	*"We recommend C1-INH as the preferred therapy for HAE attacks during pregnancy and lactation"* (p. 1587). GOE: D (adapted from existing consensus document) SOR: Strong (100% agreement) Background: *"Long-term prophylaxis may become indicated during pregnancy, especially in women experiencing an increase of attack frequency. In these women, C1-INH concentrate is considered a safe and effective treatment option. Antifibrinolytics may be considered if C1-INH concentrate is unavailable, but efficacy is not proven. Androgens are contraindicated, as these drugs cross the placenta"* (p. 1587).

	2019 International/Canadian Guideline[4]	2017 WAO/EAACI Guideline[30]
LTP in pediatric patients	Recommendation: *"When long-term prophylaxis is indicated in paediatric patients, pdC1-INH is the treatment of choice"* (p. 17). LOE: Consensus (100% agreement) SOR: Strong (97.5% agreement) Background: *"Pooled data from an RCT and its open-label extension study demonstrated that pdC1-INH was effective and well tolerated for routine prophylaxis in children with HAE"* (p. 17). Recommendation: *"Androgens should not be used for long-term prophylaxis in paediatric patients"* (p. 17). LOE: Moderate (87.1% agreement) SOR: Strong (84.62% agreement) Background: *"Androgens are known to cause premature closure of the epiphyses, among other significant side effects, and are therefore contraindicated as LTP in the paediatric population before Tanner stage 5. (…) If androgen use is necessary, paediatric patients should start at the lowest effective dose. They should have regular monitoring for side effects"* (p. 17).	No relevant recommendation. Background: *"The indications for long-term prophylaxis in adolescents are the same as in adults. The preferred therapy for long-term prophylaxis is pdC1-INH. The dosing interval and dose may need to be adjusted according to the individual response.* *"When C1-INH concentrate is not available for long-term prophylaxis, antifibrinolytics (i.e., tranexamic acid 20-40 mg/kg) are preferred to androgens because of their better safety profile; however, efficacy is questioned by many, and data are not available supporting its use. (…) Androgens are not recommended for long-term prophylaxis in children and adolescents prior to Tanner Stage V; however, long-term use has been reported, and in some cases, the benefits may outweigh the risks. The administration of androgens requires careful safety monitoring"* (p. 1586).

C1-INH = C1-esterase inhibitor; EAACI = European Academy of Allergy and Clinical Immunology; GOE = grade of evidence; HAE = hereditary angioedema; HAE-1/2 = hereditary angioedema type 1 or type 2; IV = intravenous; LOE = level of evidence; LTP = long-term prophylaxis; pdC1-INH = plasma-derived C1-esterase inhibitor; QoL = quality of life; RCT = randomized controlled trial; SC = subcutaneous; SOR = strength of recommendation; WAO = World Allergy Organization.

Source: The International/Canadian Hereditary Angioedema Guideline (2019)[4] and the International WAO/EAACI Guideline for the Management of Hereditary Angioedema (2017).[30]

Appendix 3: Summary of Reimbursement Criteria From Other Jurisdictions

Table 21: Summary of Reimbursement Recommendations for Long-Term Prophylaxis

	NHS England Clinical Commissioning Policy[35]	NICE Final Appraisal Document	Australian Government MSAC[36]
Treatment	Plasma-derived C1-INH for prophylactic treatment of HAE types 1 and 2	Lanadelumab for preventing recurrent attacks of HAE	C1-INH concentrate for hereditary angioedema
Initiation	Plasma-derived C1-INH will be commissioned for: • individuals who fail, or are intolerant of, oral prophylaxis and who experience two or more clinically significant attacks[a] per week, despite oral prophylaxis,[b] over a period of at least 56 days requiring treatment with C1-INH or icatibant, or • individuals for whom oral prophylaxis is contraindicated (e.g., pregnant women)	Lanadelumab is recommended as an option in people aged 12 and older if they are eligible for preventive C1-INH treatment, in line with the NHS England Clinical Commissioning Policy	*"MSAC considered that routine prophylaxis would be likely to be acceptably cost-effective if limited to those individuals who suffer from at least 8 attacks per month without routine prophylaxis. In the absence of clear arrangements to reinforce such a limitation, MSAC recommended that the JBC/NBA work with ASCIA to develop guidelines and governance arrangements for second-line use of C1-INH as routine prophylaxis (see Figure 2 on page 13), that reflects this limitation."* (p. 3)
Prescribing conditions	*"Long-term, prophylactic C1-INH injections should be considered by specialist immunology consultants working in specialist centres, with approval from their respective networks (see Clinical Governance in Immunology Service Specification B09/S/a). Use should be in line with the Marketing Authorisation. Use outside of this will not be funded."* (p. 15) *"Each patient considered for treatment with long-term prophylactic C1-inhibitor injections will have their case assessed by the specialist immunology network to ensure that it is the most appropriate treatment option. Eligibility for treatment will be based on discussion between at least three consultant immunologists either at a regional network meeting or discussion by email or telephone. At least two of these consultants will be from centres different to the host centre. A host centre which is exclusively staffed by non-immunologists will need to liaise with immunologists locally and from other centres."* (p. 16)		

	NHS England Clinical Commissioning Policy[35]	NICE Final Appraisal Document	Australian Government MSAC[36]
Discontinuation	*"If treatment is ineffective after two months (defined as a lack of reduction in attack frequency despite optimised treatment) then treatment with prophylactic C1-inhibitor should be discontinued and alternative therapy options considered"* (p. 16).		
Dosage adjustments	*"After the first six months of treatment, the time between dosing should be gradually increased. If, at a dosing interval of one treatment per week, the symptoms remain below two or more clinically significant attacks per week a trial of treatment discontinuation should be commenced. If breakthrough attacks present above this level, the time between dosing should be reduced to regain adequate symptom control"* (p.16).	*"[T]he lowest dosing frequency of lanadelumab is used in line with the summary of product characteristics, that is, when the condition is in a stable, attack-free phase"* (p. 1).	

ASCIA = Australasian Society of Clinical Immunology and Allergy; C1-INH = C1-esterase inhibitor; HAE = hereditary angioedema; JBC = Jurisdictional Blood Committee; MSAC = Medical Services Advisory Committee; NBA = National Blood Authority; NHS = National Health Services; NICE = National Institute for Health and Care Excellence.

[a] "*A clinically significant attack is one which is i) potentially life threatening because it affects the head or neck or ii) causes pain or disability such that the patient cannot continue their normal activities. This may be due to disabling cutaneous swelling, sufficient to prevent the patient from undertaking normal activities or severe abdominal pain which will not respond to oral analgesia. Varying treatment pathways do not imply that an attack requiring hospital treatment is necessarily more significant than one which can be treated with self-administered therapies.*"[35]

[b] Oral prophylaxis refers to androgens or antifibrinolytics.

Source: NHS Clinical Commissioning Policy,[35] NICE Final Appraisal Document,[40] and MSAC Public Summary Document.[36]

Table 22: Summary of US Coverage Policies for Long-Term Prophylaxis

	Aetna[41]	Anthem Blue Cross[42]	California DHCS[43]	Cigna[44]	Centene[45]	Premera Blue Cross[46]
Relevant Treatment(s)	Cinryze, Haegarda, Takhzyro	Cinryze, Haegarda, Takhzyro	Haegarda	Cinryze, Haegarda, Takhzyro	Cinryze, Haegarda	Cinryze, Haegarda, Takhzyro
Initiation Criteria						
Age	Cinryze: ≥ 6 years Haegarda and Takhzyro: ≥ 12 years	Cinryze: ≥ 6 years Haegarda and Takhzyro: ≥ 12 years	≥ 12 years	NA	Cinryze: ≥ 6 years Haegarda: ≥ 12 years	Haegarda and Takhzyro: ≥ 12 years
Confirmed HAE diagnosis	Yes	Yes	Yes	Yes	Yes	Yes, type 1 or 2

	Aetna[41]	Anthem Blue Cross[42]	California DHCS[43]	Cigna[44]	Centene[45]	Premera Blue Cross[46]
HAE history	≥ 1 attack/month	Moderate or severe attacks	≥ 1 moderate or severe attack/month	≥ 2 moderate or severe attacks/ month	≥ 1 of: • > 1 severe event per month, or • disabled for > 5 days per month, or • has a history of previous airway compromise	≥ 2 of: • recurrent angioedema without wheals or urticaria • recurrent abdominal attacks • positive family history • failure to respond to antihistamines, glucocorticoids, or epinephrine
Medications known to cause angioedema have been evaluated and discontinued, when appropriate	Yes		Yes	Yes		
Has tried (and failed or is intolerant to) or has a contraindication to other drugs for HAE prophylaxis	All treatments: Yes, 17 alpha-alkylated androgens or antifibrinolytic drugs Cinryze and Takhzyro: Yes Haegarda: If ≥ 12 years in age	Yes, 17 alpha-alkylated androgens or antifibrinolytic drugs	Yes, alternative long-term prophylaxis treatments		For post-pubertal adolescents and adults: yes, danazol	Yes, danazol or another androgen
Concomitant treatments for HAE	Concomitant use of Cinryze, Haegarda, and/or Takhzyro is considered experimental and investigational for all indications because its safety and effectiveness has not been established		Will not be administered in conjunction with other approved treatments for acute HAE attacks	Cinryze, Haegarda, and Takhzyro will not be used concomitantly		Not used concomitantly with other targeted HAE-specific therapies for prophylactic treatment

	Aetna[41]	Anthem Blue Cross[42]	California DHCS[43]	Cigna[44]	Centene[45]	Premera Blue Cross[46]
Prescribing conditions			Maximum dosage is 3,000 units; claims billed for higher quantities require documentation that patient's weight exceeds 150 kg.		• Prescribed by or in consultation with a hematologist, allergist, or immunologist • Dose does not exceed 2,500 units every 3 to 4 days for Cinryze, or 60 IU/kg twice weekly for Haegarda	
Renewal criteria					• Reduction in attacks from baseline, or request is for a dose increase • Approval duration of 12 months	• Has shown and continues to show a reduction in baseline frequency of attacks (in addition to the preceding criteria) • Initial approval duration of 3 months; 1 year for continued therapy

DHCS = Department of Health Care Services; HAE = hereditary angioedema; NA = not available.

Source: Coverage policies for Aetna,[41] Anthem Blue Cross,[42] California DHCS,[43] Cigna,[44] Centene,[45] and Premera Blue Cross.[46]

Appendix 4: CADTH Adaptation of Institute for Clinical and Economic Review Economic Evaluation

Methods

CADTH adapted an existing economic evaluation conducted by the Institute for Clinical and Economic Review (ICER)[2] to assess the lifetime costs, health outcomes, and cost-effectiveness of long-term prophylaxis (LTP) of hereditary angioedema (HAE) compared with no prophylaxis. The perspective of the ICER model was that of the US health care system; however, the economic model was adapted by CADTH to reflect a Canadian context.

The target population of the ICER model consisted of HAE patients in the US who are candidates for LTP. The baseline age, gender, and attack frequency of the model population were based on the weighted average across the three pivotal clinical trials for the interventions,[24-26] whereas the baseline weight for the model population was obtained from the US Centers for Disease Control and Prevention anthropometric data.[47] The analysis compared the total costs and quality-adjusted life-years (QALYs) of the three drugs approved for LTP of HAE in the US (lanadelumab, Cinryze intravenous [IV], and Haegarda) with no LTP treatment. On-demand treatment for acute attacks consisted of treatment with the following drugs approved in the US: Berinert, ecallantide, icatibant, and conestat alfa. An annual discount rate of 3% was applied to both costs and benefits to reflect the US health care system perspective over a lifetime horizon. A complete description of the model can be found in the ICER report.[2] CADTH adapted the model to a Canadian context and excluded conestat alfa and ecallantide from the analysis, as these therapies are not currently approved in Canada; furthermore, CADTH used Canadian sources for the costs and set the discount rate to 1.5%, as per Canadian guidelines.[3]

Data Inputs

Treatment effects were based on the pivotal trials of each LTP therapy,[24-26] whereas the severity and anatomical location of acute attacks were estimated from the Berinert Patient Registry[48] (a multi-centre, observational study conducted to obtain safety and usage data on patients receiving Berinert). Berinert is considered to have the same efficacy as Berinert for LTP, based on clinical expert feedback. Use of Haegarda was assumed to alter the distribution of attack severity, according to data from the COMPACT study.[25]

Treatment patterns for acute HAE attacks were estimated from a survey of US physicians.[49] Only laryngeal attacks were assumed to be fatal; the monthly probability of death from a laryngeal attack was based on an Italian study of patients with HAE receiving on-demand therapy.[50] Details on model parameter values can be found in Table 23.

Table 23: Clinical and Baseline Demographic Inputs

Input	Value	Distribution	Source	Note
Baseline Demographic Inputs				
Age	39.6	Normal	Weighted average of the baseline characteristics across the pivotal clinical trials for the interventions[24-26]	These inputs have been validated by the clinical expert consulted by CADTH; however, the clinical expert noted that patients with few but extremely disabling attacks would not be reflected in this population.
Gender (% female)	68.4	Beta		
Baseline attack frequency (per month)	3.39	Normal		
Weight, female (kg)	76.4 (SD: 30.93)	Normal	Centers for Disease Control and Prevention (CDC) anthropometric reference data[47]	
Weight, male (kg)	88.8 (SD: 31.11)	Normal		
Clinical Inputs				
Pre-treatment severity of attack: Mild Moderate Severe Laryngeal involvement if severe	 36.6% 46.2% 17.2% 11.5%	 Dirichlet Dirichlet Dirichlet Beta	Berinert patient registry[48]	Laryngeal involvement was back-calculated in order to match the % of laryngeal attacks in the Berinert Patient Registry[48] (2%).
Percentage mean reduction in attack frequency: Lanadelumab Cinryze Haegarda	 86.9% 50.5% 84.0%	Beta	Pivotal trials of each LTP therapy[24-26]	These inputs have been validated by the CADTH clinical reviewer.
Post-treatment adjustment of severity distribution: Haegarda (versus mild) Moderate Severe	 −0.556 −1.307	Normal	Lumry et al., COMPACT study[51]	The coefficients were used to adjust for post-treatment severity distribution.
Percentage attack-free post-treatment: Lanadelumab (300 mg q.2.w.) Lanadelumab (300 mg q.4.w.) Cinryze Haegarda	 44% 31% 18% 40%	Beta	Pivotal trials of each LTP therapy[24-26]	These inputs have been validated by the CADTH clinical reviewer.
Percentage of patients on on-demand therapy who require an extra dose: Cinryze Berinert Firazyr	 10% 1.9% 12.7%	Beta	Assumption Zanichelli et al., 2015[52] Zanichelli et al., 2015[52]	The assumption of 10% of patients on Cinryze requiring an extra dose has been validated by the clinical expert; however, the clinical expert noted this proportion may be low if the dose is not accurately adjusted. The analysis therefore assumes all doses are accurately adjusted

Input	Value	Distribution	Source	Note
Mode of Treatment Administration				
Mild and moderate: Self Home nurse Outpatient ED	 64.9% 13.8% 21.3% 0%	–	Riedl et al., 2011[49]	ICER assumed only, and all, severe attacks are treated in the ED. This assumption was validated by CADTH's clinical expert.
Severe, laryngeal, and non-laryngeal: Self Home nurse Outpatient ED	 0 0 0 100%	–	Assumption	
Hospitalization: Mild Moderate Severe, laryngeal Severe, non-laryngeal	 0 0 40.9% 40.9%	Beta	Zilberberg et al., 2011[53]	This assumption was considered appropriate by CADTH reviewers.
Mortality				
Case fatality rate from laryngeal attack	0.0000217	Beta	Bork et al., 2012[54]	ICER assumed that only laryngeal attacks could be fatal. The clinical expert consulted by CADTH noted that abdominal attacks could also be fatal. Abdominal attacks are not included in the model and as such this remains a limitation of the analysis.
Percentage of patients who are hospitalized	69.4%			
Percentage of hospitalized patients getting cricothyrotomy	40.0%			
Percentage of hospitalized patients who are intubated	60.0%			
Percentage of cricothyrotomy patients who receive artificial respiration	40.0%			
Percentage of intubated patients who receive artificial respiration	26.7%			

ED = emergency department; ICER = Institute for Clinical and Economic Review; LTP = long-term prophylaxis; q.2.w. = once every two weeks; q.4.w. = once every four weeks; SD = standard deviation.

Utilities

Utility values were estimated from a Swedish study of HAE patients experiencing acute attacks.[27] Estimates from this study were used to build a baseline utility function dependent on age and number of attacks. This function was used to calculate the baseline utility of patients who experience acute attacks, whereas the difference between the EuroQol 5-Dimensions questionnaire (EQ-5D) scores during the attack-free state and the EQ-5D scores during HAE attacks were used to estimate the attack disutility for mild, moderate, and severe attacks.

Table 24: Utility Inputs

Health State	Mean	Distribution	Source
Attack-free utility	0.825	Beta	Nordenfelt et al., 2014[27]
Effect of age on base utility	−0.02205	Normal	
Effect of number of attacks on base utility	−0.0043	Normal	
Attack disutility			
Mild	0.070	Beta	
Moderate	0.369	Beta	
Severe	0.486	Beta	

Costs

All costs in the ICER model were from the US health care system perspective and were inflated to 2018 US dollars. CADTH obtained physician, emergency department, and administration costs from the Ontario Schedule of Benefits. Drug acquisition costs for lanadelumab and icatibant were estimated from BC PharmaCare lanadelumab drug information[33] and the IQVIA database, respectively, whereas drug acquisition costs for Cinryze, Berinert, and Haegarda were provided by Canadian Blood Services. All costs were reported in Canadian dollars and can be found in Table 26.

Model Assumptions

Key model assumptions are listed in Table 25.

Table 25: Key Model Assumptions (Source: Institute for Clinical and Economic Review Report)

Assumption	Rationale
HAE-specific mortality results only from asphyxiation following a laryngeal attack; other anatomical locations for acute attacks do not result in death or permanent disability.	Death from HAE attacks primarily results from asphyxiation following a laryngeal attack.[54] We found no evidence that HAE attacks result in permanent disability.
Death due to asphyxiation following a laryngeal attack occurs quickly following the attack; we will assume that these patients do not receive on-demand treatment.	The mean (standard deviation) duration of a fatal laryngeal attack is 4.5 (3.6) hours.[54] In Bork et al., 2008, whether on-demand therapy had been administered to patients who subsequently died following a laryngeal attack was unclear.
All non-fatal moderate and severe acute attacks are treated (varied in sensitivity analysis).	Treatment guidelines and empirical data suggest that moderate and severe attacks are treated.[55]
Only (and all) severe attacks are treated in the ED.	Treatment guidelines and empirical data suggest that severe attacks are typically treated in the ED.[55]
Non-severe attacks do not result in ED visits or hospitalizations.	Treatment guidelines and empirical data suggest that non-severe attacks are not typically treated in the ED nor do they result in hospitalizations.[55]
Mild and moderate attacks last one day; severe attacks last two days. Untreated attacks last an extra day.	Data on the duration of attacks by severity is limited. One study in Italy suggests there is no difference in the mean duration between mild and moderate attacks, but there is a trend toward an increased duration of severe attacks. Untreated attacks lasted longer than treated attacks.[56]
Patients do not discontinue LTP therapies over their lifetime.	There is no indication that attack rate declines with age.

Assumption	Rationale
Adverse events (AEs) related to these drugs do not lead to substantial incremental costs or disutilities.	There were no serious or treatment-related AEs attributable to the LTP therapies in the clinical trials.
We did not model short-term prophylaxis for dental procedures or other episodes.	There is limited data to inform the frequency and/or timing of short-term prophylaxis.

AE = adverse event; ED = emergency department; HAE = hereditary angioedema; LTP = long-term prophylaxis.

Source: Institute for Clinical and Economic Review report.

Changes to Institute for Clinical and Economic Review Model

Table 26: Changes to Model Inputs

Parameter	ICER Model	CADTH Base Case	Rationale	Source
Settings				
Discount rate	3%	1.5%	Costs and outcomes should be discounted to present values at a rate of 1.5% per year as per CADTH guidelines.	CADTH guidelines.[3]
Market Shares of On-Demand Drugs				
Self-administered: Cinryze Berinert Ecallantide Icatibant Conestat alfa	 0% 33.3% 0% 33.3% 33.3%	 6% 88% 0% 6% 0%	Conestat alfa and ecallantide are not approved by Health Canada and need to be excluded from the analysis. Therefore, CADTH has set the market shares for these products to 0%. Furthermore, on-demand drugs are either self-administered or administered in the emergency department in Canada, according to clinical expert feedback. Note that even though Cinryze is only indicated for LTP, the clinical expert consulted by CADTH noted that a small proportion of patients who receive Cinryze prophylactically may also take it on-demand to treat attacks.	CADTH clinical expert.
Nurse-administered: Cinryze Berinert Ecallantide Icatibant Conestat alfa	 0% 33.3% 0% 33.3% 33.3%	 0% 0% 0% 0% 0%		
Physician-administered: Cinryze Berinert Ecallantide Icatibant Conestat alfa	 0% 25% 25% 25% 25%	 0% 0% 0% 0% 0%		
Emergency department–administered: Cinryze Berinert Ecallantide Icatibant Conestat alfa	 0% 25% 25% 25% 25%	 0% 99% 0% 1% 0%		

Parameter	ICER Model	CADTH Base Case	Rationale	Source
Costs				
Direct Costs				
Drug administration per acute attack: Self Home nurse Physician office	 US$0 US$177 US$262	 C$0 C$39.23 C$157	Canadian costs should be used when available in order to reflect the Canadian context.	Average nurse hourly rate from Ontario Nurses' Association.[57] Physician costs from Schedule of Benefits code A615.
Emergency department	US$1,479	C$97.60		Schedule of Benefits code H055.
Hospitalization	US$4,760	C$1,175		OCCI code R609.
Drug Acquisition Costs[a]				
Lanadelumab (300 mg) Cinryze (500 IU) Haegarda 2,000 IU Haegarda 3,000 IU Berinert (20 units/kg)[b] Firazyr (30 mg)	US$16,520 US$2,012 US$1,393 US$2,090 US$4,174 US$7,178	C$20,538 [redacted] C$2,700	Canadian costs should be used when available in order to reflect the Canadian context. Costs provided by CBS for Cinryze, Haegarda, and Berinert were converted to Canadian dollars.[c]	Costs for lanadelumab were back-calculated from BC PharmaCare lanadelumab drug information.[33] Source for icatibant is the IQVIA database. Costs for Cinryze, Haegarda, and Berinert were provided by CBS.
Other Costs				
Physician office visit	US$80	C$70.90	Canadian costs should be used when available in order to reflect the Canadian context.	Schedule of Benefits code A611.
Subcutaneous administration	US$20.88	C$6.75		Schedule of Benefits code G373.
IV administration	US$47.16	C$54.3		Schedule of Benefits code G381 standard chemo as proxy.
Intubation, endotracheal emergency	US$146	C$38.35		Schedule of Benefits code G211.
Cricothyrotomy	US$347	C$474.65		Schedule of Benefits code Z325 emergency tracheotomy as proxy.
Respiratory system diagnosis with ventilator support	< 96 hours US$14,809 > 96 hours US$32,709	First day: C$193.45 Second to 30th day: C$101.55 31st day onward: C$67.6		Schedule of Benefits codes G405 and G406.

CBS = Canadian Blood Services; HAE = hereditary angioedema; IV = intravenous; LTP = long-term prophylaxis; OCCI = Ontario Case Costing Initiative.

[a] US drug costs obtained from the Federal Supply Schedule as of September 15, 2018.

[b] Cost per administration.

[c] Currency converted based on Bank of Canada rates (https://www.bankofcanada.ca/rates/exchange/currency-converter/) for the month of September 2019 (C$1 = US$0.75).

Results

CADTH Base Case

The probabilistic results characterize the extent to which parameter uncertainty affects the cost-effectiveness estimates in the model. Standard distributional forms were taken to describe the probability distribution functions relating to input parameters (age and weight were characterized by normal distributions, utility and binary proportions were characterized by beta distribution, multinomial categorical variables were characterized by Dirichlet distributions, costs were characterized by gamma distributions, and baseline attack rate and percentage mean reductions in attack rate were characterized by log-normal distributions).

In the CADTH base case, no LTP was associated with total costs of $9,172,106, whereas Cinryze, lanadelumab, and Berinert were associated with costs of $9,827,239, $17,363,457, and $24,468,170, respectively. Detailed cost results can be found in Table 27.

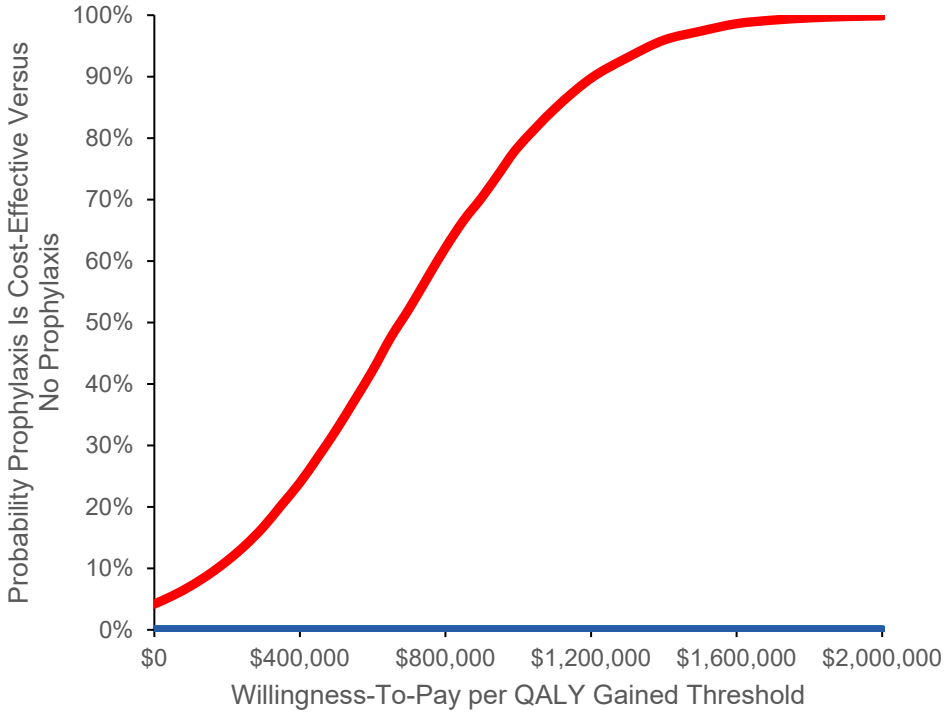
Table 27: Detailed Cost Results

Treatment	LTP Drug Costs ($)	Acute Treatment Costs (Drugs) ($)	Acute Treatment Costs (Other Services) ($)	Total Costs ($)
No LTP	0	8,990,628	181,477	9,172,106
Cinryze	5,284,779	4,452,559	89,901	9,827,239
Lanadelumab	16,158,210	1,181,400	23,846	17,363,457
Berinert	23,085,522	1,363,906	18,742	24,468,170

LTP = long-term prophylaxis.

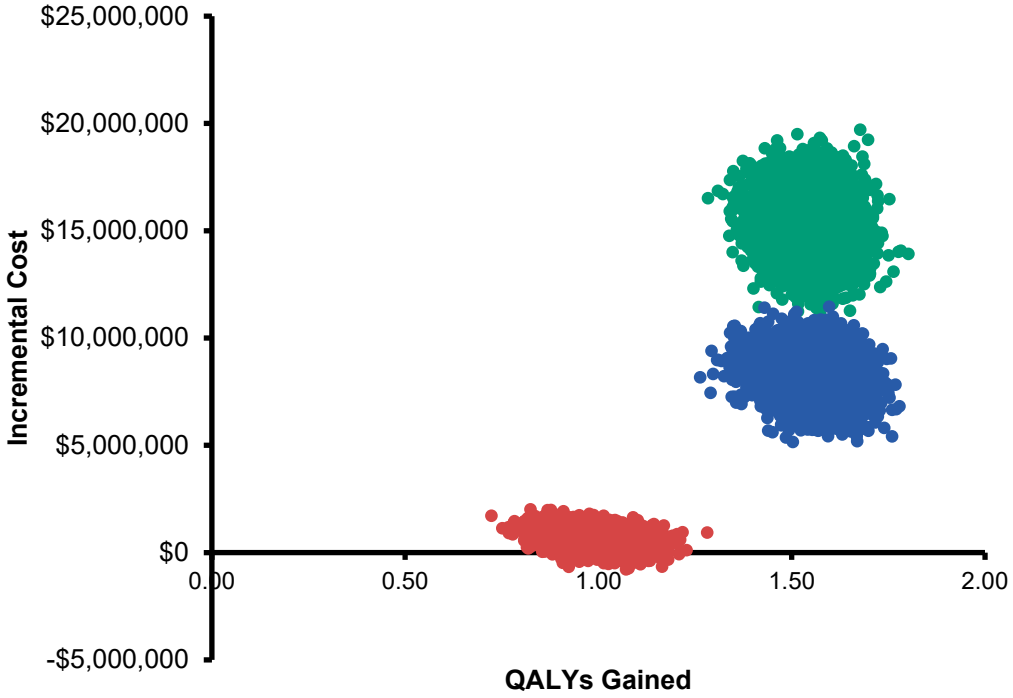
A scatterplot was produced to illustrate the results of the base-case simulations (Figure 12). The cost-effectiveness scatterplot diagram shows the differences in clinical and cost outcomes for LTP versus no LTP. A cost-effectiveness acceptability curve was then produced by calculating the proportion of data points below willingness-to-pay (WTP) thresholds of up to $2,000,000. Where a decision-maker is willing to pay between $50,000 and $2,000,000 per QALY gained, Cinryze had the highest probability of being cost-effective versus no LTP; lanadelumab and Berinert had a 0% probability of being cost-effective versus no LTP, whereas Cinryze had a 3% probability of being cost-effective at a WTP threshold of $150,000. (Figure 11). The cost-effectiveness acceptability curve and scatterplot can be found in Figure 11 and Figure 12, respectively.

Figure 11: Cost-Effectiveness Acceptability Curve



QALY = quality-adjusted life-year.
Berinert = green; lanadelumab = blue; Cinryze = red.

Figure 12: Cost-Effectiveness Scatterplot



QALY = quality-adjusted life-year.
Berinert = green; lanadelumab = blue; Cinryze = red.

Exploratory Analyses

Probabilistic scenario analyses were conducted that varied model parameters and assumptions and included the following: inclusion of Haegarda as comparator (at the cost submitted by Canadian Blood Services, as well as alternative costs); alternative monthly attack rates (rate of 1 to 10 attacks per month); alternative duration of attacks (attacks take 48 hours to resolve if treated, 72 hours if untreated); alternative dosing for lanadelumab; and a societal perspective. Price-reduction scenarios were also conducted.

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

- Inclusion of Haegarda as comparator at a cost equal to Cinryze: Both no LTP and Cinryze are dominated by Haegarda (Haegarda is associated with lower costs and higher QALYs), and the ICUR for lanadelumab versus no LTP increased to $1,225,384,912.
- Assuming all attacks take 48 hours to resolve if treated, and 72 hours if untreated: The ICUR for Cinryze versus no LTP decreased to $284,233, whereas the ICUR for lanadelumab versus Cinryze decreased to $9,470,001.

A summary of exploratory analyses can be found in Table 15, and detailed results for all exploratory analyses can be found in Table 28 to Table 34.

Table 28: CADTH Exploratory Analyses – Inclusion of Haegarda as Comparator (Assuming Cost of Haegarda Is Equal to the Cost of Cinryze)

Therapy	Expected Costs ($)	Expected QALYs	Incremental Costs ($)	Incremental QALYs	Sequential ICUR, $/QALY Gained
Haegarda	8,704,659	24.1376			
No prophylaxis	9,164,753	22.5908	460,095	−1.5468	Dominated
Cinryze	9,818,926	23.5649	654,172	0.9742	Dominated
Lanadelumab	17,336,485	24.1447	7,517,559	0.5797	$1,225,384,912
Berinert	24,479,847	24,1006	7,143,362	−0.0441	Dominated

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

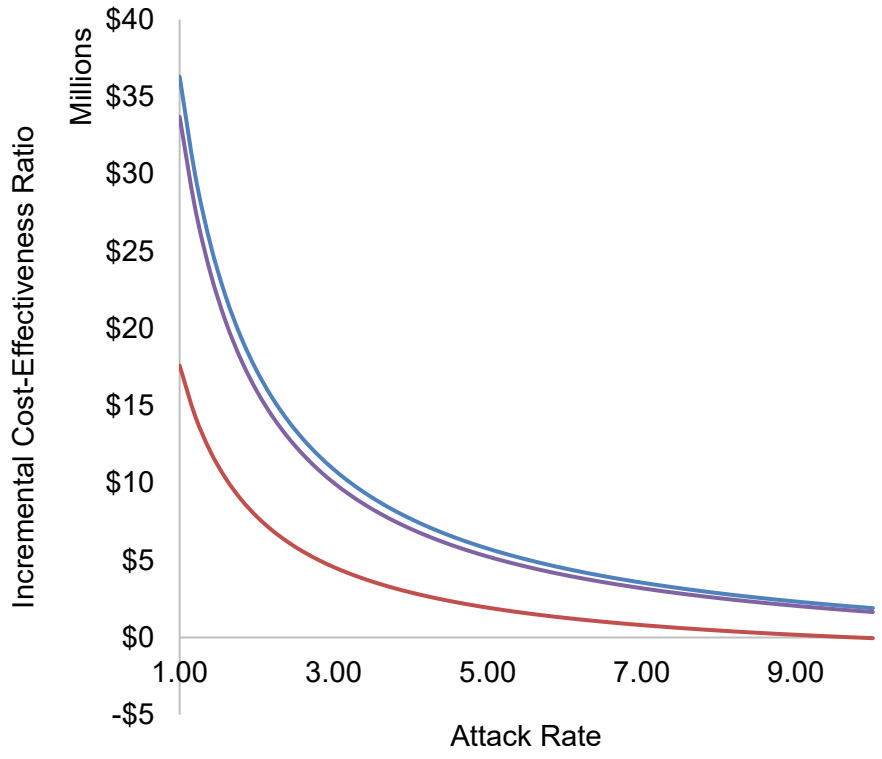
Table 29: CADTH Exploratory Analyses – Alternative Dosing for Berinert

Scenario	Therapy	Expected Costs ($)	Expected QALYs	Incremental Costs ($)	Incremental QALYs	Sequential ICUR, $/QALY Gained ($)
90% of patients receive off-label Berinert subcutaneously (60 IU/kg dose), 10% receive it intravenously (20 IU/kg dose)	No LTP	9,169,712	22.5876			
	Cinryze	9,818,180	23.5613	648,468	0.9737	665,975
	Lanadelumab	17,356,894	24.1381	8,187,182	1.5505	13,070,542
	Berinert	22,937,218	24.1354	13,767,506	1.5478	Dominated
75% of patients receive off-label Berinert subcutaneously (60 IU/kg dose), 25% receive it intravenously (20 IU/kg dose)	No LTP	9,168,757	22.5606			
	Cinryze	9,825,101	23.5329	656,344	0.9723	675,046
	Lanadelumab	17,339,038	24.1123	8,170,281	1.5517	12,968,943
	Berinert	20,664,537	24.1054	11,495,780	1.5448	Dominated
50% of patients receive off-label Berinert subcutaneously (60 IU/kg dose), 50% receive it intravenously (20 IU/kg dose)	No LTP	9,166,163	22.5807			
	Cinryze	9,820,662	23.5527	654,499	0.9721	673,300
	Berinert	16,779,605	24.1264	7,613,442	1.5457	12,131,111
	Lanadelumab	17,351,916	24.1310	8,185,753	1.5504	$123,543,779

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Figure 13 shows the rate of monthly attacks that would allow each LTP therapy to reach cost-effectiveness thresholds of $50,000, $100,000, and $150,000 per QALY. An attack rate of 9.6, 9.3, and 9.1 per month would allow Cinryze to reach cost-effectiveness thresholds of $50,000, $100,000, and $150,000 per QALY, respectively.

Figure 13: Incremental Cost-Effectiveness Ratios Versus Attack Rate



Berinert = blue; lanadelumab = purple; Cinryze = red

Based on clinical expert feedback, CADTH explored the impact of assuming all attacks take 48 hours to resolve if treated, and 72 hours if untreated. Results can be found in Table 30.

Table 30: CADTH Exploratory Analyses – Mild, Moderate and Severe Attacks Take 48 Hours to Resolve if Treated, and 72 Hours if Untreated

Therapy	Expected Costs ($)	Expected QALYs	Incremental Costs ($)	Incremental QALYs	Sequential ICUR, $/QALY Gained ($)
No prophylaxis	9,163,495	21.8961			
Cinryze	9,553,404	23.2679	389,909	1.3718	284,233
Lanadelumab	17,146,869	24.0697	7,593,464	0.8018	9,470,001
Berinert	24,068,607	24.0643	6,921,738	−0.0054	Dominated

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

An additional exploratory analysis assumed a dosing schedule of every four weeks would be attempted for 44% of patients, with only 31% remaining attack-free on this dosing at six months and beyond. Results can be found in Table 31.

Table 31: CADTH Exploratory Analyses – Alternative Dosing for Lanadelumab

Therapy	Expected Costs ($)	Expected QALYs	Incremental Costs ($)	Incremental QALYs	Pairwise ICUR, $/QALY Gained ($)	Sequential ICUR, $/QALY Gained ($)
No LTP	9,176,195	22.5656				
Cinryze	9,821,157	23.5385	644,962	0.9729	662,904	662,904
lanadelumab	17,368,110	24.1185	7,546,954	0.5800	5,275,139	13,012,114
Berinert	24,439,064	24.0922	7,070,954	−0.0263	9,997,949	Dominated

ICUR = incremental cost-utility ratio; LTP = long-term prophylaxis; QALY = quality-adjusted life-year.

Price-reduction analyses were conducted to estimate the maximum prices required to achieve WTP thresholds of $50,000, $100,000, $150,000, $200,000, $300,000, and $500,000 per QALY. Threshold prices are shown in Table 32.

Table 32: CADTH Threshold Analyses – Required Prices per Therapy to Achieve WTP Thresholds of $50,000, $100,000, $150,000, $200,000, $300,000, and $500,000 per QALY

Therapy	Price Required to Achieve WTP Threshold					
	$50,000 per QALY ($)	$100,000 per QALY ($)	$150,000 per QALY ($)	$200,000 per QALY ($)	$30,000 per QALY ($)	$500,000 per QALY ($)
Cinryze	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab	3,764	3,863	3,962	4,060	4,258	4,653
Berinert	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

QALY = quality-adjusted life-year; WTP = willingness to pay.

Productivity costs, including lost wages for patients and out-of-pocket expenses for acute attacks, were included in an exploratory analysis. Results can be found in Table 33, and detailed cost results in Table 34.

Table 33: CADTH Exploratory Analyses – Societal Perspective

Therapy	Expected Costs ($)	Expected QALYs	Incremental Costs ($)	Incremental QALYs	Pairwise ICUR, $/QALY Gained ($)	Sequential ICUR, $/QALY Gained ($)
No LTP	9,427,431	22.6003				
Cinryze	9,945,157	23.5709	517,726	0.971	533,392	533,392
Lanadelumab	17,367,203	24.1525	7,939,772	1.552	5,115,225	12,762,387
Berinert	24,488,470	24.1227	7,121,267	−0.0298	9,892,958	Dominated

ICUR = incremental cost-utility ratio; LTP = long-term prophylaxis; QALY = quality-adjusted life-year.

Table 34: Detailed Cost Results – Societal Perspective

Treatment	LTP Drug Costs ($)	Acute Treatment Costs (Drugs) ($)	Acute Treatment Costs (Other Services) ($)	Indirect Costs ($)	Total Costs ($)
No LTP	0	8,992,554	179,872	255,005	9,427,431
Cinryze	5,281,126	4,448,853	89,022	126,156	9,945,157
Lanadelumab	16,142,111	1,168,503	23,449	33,141	17,367,203
Berinert	23,095,381	1,343,559	18,394	31,136	24,488,470

LTP = long-term prophylaxis.

Appendix 5: Budget Impact Analysis

Detailed information regarding the budget impact analysis is provided in the main body of the report. Table 35 and Table 36 provide additional supplementary information regarding inputs and the results of the budget impact analysis.

Table 35: Monthly and Annual Attack Frequency Associated With Long-Term Prophylaxis Treatments

Treatment	Percentage Reduction in Attack Frequency (%)	Number of Attacks per Month	Annual Number of Attacks
Berinert	84.0	0.54	6.51
Cinryze	50.5	1.68	20.14
Haegarda	84.0	0.54	6.51
Lanadelumab	86.9	0.44	5.33
No LTP: Patients requiring LTP	0	3.39	40.68
No LTP: Patients not requiring LTP	0	1.34	16.08

LTP = long-term prophylaxis.

For patients not requiring LTP, annual drug costs only included costs associated with on-demand treatment and were calculated by multiplying the cost per on-demand dose by the monthly baseline attack frequency (1.34 for patients not requiring LTP), multiplied by 12 months.

Table 36: Inputs for Base-Case Budget Impact Analysis

Parameter	Base-Case Inputs	Source	Values Explored in Scenario
Population	Canada minus Quebec (29,104,297)	Statistics Canada[22]	• Canada, including Quebec • All jurisdictions individually
Proportion of population covered by CBS	100%	Assumption	NA
Prevalence of HAE	1:67,000	Aygoren-Pursun, 2018[6]	• 1:10,000 (high-prevalence estimate)[28] • 1:35,000 (CBS estimate) • 1:50,000 (commonly cited estimate)[1] • 1:92,000 (minimal-prevalence estimate)[6]
Percentage of HAE patients diagnosed	65%	Calibration exercise to have BIA spending align with CBS spending	50%, 75%, 85%, 100%
Percentage of patients receiving treatment	92.2%	Mendivil et al., 2019[31]	80%, 100%
Number of HAE patients	282	Calculation (prevalence × population × % diagnosed)	
Number of HAE patients receiving treatment	260	Calculation (number of patients × % receiving treatment)	
Proportion of HAE patients requiring LTP	41%	Mendivil, 2019[31]	30%, 50%, 60%, 70%, 80%, 90%, 100%
Number of HAE patients requiring LTP	107	Calculation (patients receiving treatment × % requiring LTP)	
Number of HAE patients not requiring LTP	153	Calculation (patients receiving treatment × % not requiring LTP)	

Parameter	Base-Case Inputs	Source	Values Explored in Scenario
Patient weight	80.32 kg	Weighted average of CDC weights, based on % female in pivotal trials	± 10% of base-case weight
Current treatment distribution of LTP therapies	[redacted] Berinert Cinryze no LTP	Assumed market shares based on CBS feedback; with 107 patients receiving LTP, assuming 15% are using Cinryze results in 16 patients using Cinryze	NA
Percentage of patients using Berinert for LTP using it subcutaneously	75%	Clinical expert feedback indicated about 25% are using Berinert IV for LTP in clinical practice	50%, 60%, 70%, 80%, 90%, 100%
Berinert SC dose used	60 IU/kg	Clinical expert feedback	40 IU/kg
Berinert IV dose used	20 IU/kg	Clinical expert feedback	NA
Baseline attack frequency: patients requiring LTP	3.39 per month	Weighted average of baseline values across pivotal trials	2, 4, 5, 5 attacks per month
Baseline attack frequency: patients not requiring LTP	1.34 per month	Mendivil et al., 2018[31]	0, 2, 3 attacks per month
New drugs becoming accessible to patients	Both Haegarda and lanadelumab become accessible in year 1	Assumption	• Only Haegarda becomes accessible • Only lanadelumab becomes accessible • Haegarda replaces Berinert LTP (100%, 85%) • Haegarda replaces Berinert SC LTP (100%, 85%)
Predicted Haegarda market share in year 1, 2, and 3	[redacted]	Clinical expert feedback	Different market shares explored: [redacted] lanadelumab does not enter, Haegarda replaces all Berinert for LTP, Haegarda replaces 85% of Berinert for LTP, Haegarda replaces all Berinert SC for LTP, Haegarda replaces 85% of Berinert SC for LTP
Predicted lanadelumab market share in year 1, 2, and 3	[redacted]	Clinical expert feedback	Different market shares explored: [redacted] Haegarda does not enter
All acute attacks are treated	True	Assumption	Explored in scenario: treating only 80%, 90% of acute attacks

BIA = budget impact analysis; C1-INH = C1-inhibitor; CBS = Canadian Blood Services; CDC = Centers for Disease Control; HAE = hereditary angioedema; LTP = long-term prophylaxis; IV = intravenous; NA = not applicable; SC = subcutaneous.

Jurisdictional Budget Impact

CADTH attempted to estimate the costs associated with treating hereditary angioedema within each jurisdiction, excluding Quebec, by multiplying the population of the jurisdiction by the estimated prevalence of HAE. This analysis assumes that the prevalence of HAE is the same across jurisdictions in Canada; however, the actual number of HAE patients in each jurisdiction is unknown.

Table 37: Estimated Budget Impact of Hereditary Angioedema Long-Term Prophylaxis by Jurisdiction

Jurisdiction	Estimated Population, 2019[22]	Number of HAE Patients	Total Costs: Current Year ($)	3-Year Total: New-Drug BIA ($)	3-Year Total: No-LTP BIA ($)
Canada, excluding Quebec	29,104,297	434	81,681,027	−18,506,975	170,646,098
Newfoundland and Labrador	521,542	8	1,463,704	−331,641	3,057,937
Prince Edward Island	156,947	2	440,471	−99,800	920,221
Nova Scotia	971,395	14	2,726,214	−617,695	5,695,543
New Brunswick	776,827	12	2,180,160	−493,972	4,554,740
Ontario	14,566,547	217	40,880,923	−9,262,643	85,407,471
Manitoba	1,369,465	20	3,843,395	−870,822	8,029,531
Saskatchewan	1,174,462	18	3,296,120	−746,822	6,886,178
Alberta	4,371,316	65	12,268,071	−2,779,653	25,630,168
British Columbia	5,071,336	76	14,232,673	−3,224,785	29,734,568
Yukon, Northwest Territories, Nunavut	124,460	2	349,296	−79,142	729,741

BIA = budget impact analysis; HAE = hereditary angioedema; LTP = long-term prophylaxis.

Results of Population Scenarios

The summarized results of the approach to the scenario analyses conducted may be found in the main body of the report. Scenarios conducted on the population inputs included exploring various prevalence estimates, the percentage of patients diagnosed with HAE, and the percentage of patients requiring treatment and LTP. All scenarios influenced the number of HAE patients receiving treatment. The variability of the results of the new-drug and no-LTP budget impact analyses demonstrate the model's sensitivity to the number of HAE patients.

Table 38: Prevalence Scenarios

Estimate	Source	Number of HAE Patients	Number of Patients Diagnosed	Total Costs: Current Year ($)	3-Year Total: New-Drug BIA ($)	3-Year Total: No-LTP BIA ($)
Base case: 1:67,000	Aygoren-Pursun 2018[6]	434	282	81,681,027	−18,506,975	170,646,098
1:10,000	High estimate[28]	2,910	1,892	547,262,879	−123,996,732	1,143,328,855
1:35,000	CBS estimate	832	541	156,360,823	−35,427,638	326,665,387
1:50,000	Commonly cited in literature[1,28]	582	378	109,452,576	−24,799,346	228,665,771
1:92,000	Aygoren-Pursun 2018[6]	316	206	59,485,096	−13,477,906	124,274,876

BIA = budget impact analysis; CBS = Canadian Blood Services; HAE = hereditary angioedema; LTP = long-term prophylaxis.

Note: Negative values denote cost savings.

Table 39: Scenarios Exploring the Percentage of Patients Diagnosed With Hereditary Angioedema

Percentage of HAE Patients Diagnosed	Number of HAE Patients Diagnosed	Total Costs: Current Year ($)	3-Year Total: New-Drug BIA ($)	3-Year Total: No-LTP BIA ($)
Base case: 65%	282	81,681,027	−18,506,975	170,646,098
50%	217	62,831,559	−14,236,135	131,266,229
75%	326	94,247,338	−21,354,202	196,899,344
85%	369	106,813,650	−24,201,429	223,152,589
100%	434	125,663,118	−28,472,269	262,532,458

BIA = budget impact analysis; HAE = hereditary angioedema.

Note: Negative values denote cost savings.

Table 40: Scenarios Exploring the Percentage of Patients With Hereditary Angioedema Requiring Treatment

Percentage of HAE Patients Requiring LTP	Number of HAE Patients Requiring Treatment	Total Costs: Current Year ($)	3-Year Total: New-Drug BIA ($)	3-Year Total: No-LTP BIA ($)
Base case: 92.2%	260	81,681,027	−18,506,975	170,646,098
80%	226	70,872,908	−16,058,113	148,066,028
100%	282	88,591,135	−20,072,641	185,082,535

BIA = budget impact analysis; HAE = hereditary angioedema.

Note: Negative values denote cost savings.

Table 41: Scenarios Exploring the Percentage of Patients With Hereditary Angioedema Requiring Long-Term Prophylaxis

Percentage of HAE Patients Requiring Prophylaxis	Number of HAE Patients Requiring Prophylaxis	Total Costs: Current Year ($)	3-Year Total: New-Drug BIA ($)	3-Year Total: No-Prophylaxis BIA ($)
Base case: 41%	107	81,681,027	−18,506,975	170,646,098
30%	78	63,638,892	−13,492,589	124,862,998
50%	130	96,003,788	−22,487,649	208,104,997
60%	156	112,186,236	−26,985,178	249,725,997
70%	182	128,368,684	−31,482,708	291,346,996
80%	208	144,551,132	−35,980,238	332,967,996
90%	234	160,733,580	−40,477,767	374,588,995
100%	260	176,916,028	−44,975,297	416,209,994

BIA = budget impact analysis; HAE = hereditary angioedema.

Note: Negative values denote cost savings.

Results of Cost Scenarios

The summarized results of the approach to the scenario analyses conducted may be found in the main body of the report. Results of the scenario analyses demonstrate that due to weight-based dosing, results are sensitive to the patient weight used. In addition, results are sensitive to the percentage of patients using SC Berinert for LTP as opposed to IV Berinert, given the difference in dosing required for the two routes of administration. Finally, the budget impact results are sensitive to changes in the baseline attack frequencies for patients requiring LTP, demonstrating that, at higher attack frequencies, there are greater cost savings associated with new drugs becoming accessible to patients, and the impact of providing LTP compared with not providing LTP is less than in the base case.

Table 42: Cost Scenarios

Parameter	Base-Case Value	Alternate Value	Total Costs: Current Year ($)	3-Year Total: New-Drug BIA ($)	3-Year Total: No-LTP BIA ($)
Base case			81,681,027	−18,506,975	170,646,098
Patient weight	80.32 kg	−10%: 72.29 kg	73,940,098	−7,669,674	147,507,512
		+10%: 88.35 kg	93,292,420	−26,101,747	205,353,976
Percentage of patients using Berinert SC for LTP	75%	100%	93,292,420	−34,762,926	205,353,976
		90%	88,647,863	−28,260,546	191,470,825
		80%	84,003,305	−21,758,165	177,587,673
		70%	79,358,748	−15,255,785	163,704,522
		60%	74,714,191	−8,753,404	149,821,371
		50%	70,069,633	−2,251,024	135,938,220
Berinert SC dose	60 IU/kg	100% using 40 IU/kg	64,263,936	5,876,952	118,584,281
		20% using 40 IU/kg 80% using 60 IU/kg	78,203,902	−13,639,001	160,252,547
Baseline attack frequency: those requiring LTP	3.39	2	80,017,606	−17,377,302,	184,929,167
		4	82,411,017	−19,002,731	164,377,988
		5	83,607,723	−19,815,445	154,102,399
Baseline attack frequency: those not requiring LTP	1.34	0	72,799,530	−18,506,975	170,646,098
		2	86,055,495	−18,506,975	170,646,098
		3	92,683,478	−18,506,975	170,646,098
Percentage of acute attacks treated with on-demand therapy	100%	80%	79,093,361	−17,955,954	177,612,947
		90%	80,387,194	−18,231,465	174,129,523

BIA = budget impact analysis; LTP = long-term prophylaxis; NA: not applicable; SC = subcutaneous.

Note: Negative values denote cost savings.

Results of New-Drug Scenarios

Due to uncertainty in the uptake of new drugs, a variety of scenario analyses were explored. Larger cost savings occur when Haegarda replaces Berinert for LTP.

Table 43: Scenario Analysis on the Market Uptake of New Drugs

		Incremental Budget Impact ($)			
Scenario	**Value (Year 1, Year 2, Year 3) (%)**	**Year 1 ($)**	**Year 2 ($)**	**Year 3 ($)**	**3-Year Total ($)**
Base case	Haegarda: [redacted] Lanadelumab: [redacted]	−3,908,698	−5,308,646	−9,289,813	−18,506,975
Only Haegarda enters	Haegarda: [redacted] Lanadelumab: 0, 0, 0	−2,508,931	−2,508,931	−4,390,629	−9,408,490
	Haegarda: [redacted] Lanadelumab: 0, 0, 0	−2,508,931	−5,017,862	−7,526,792	−15,053,585
Only lanadelumab enters	Haegarda: 0, 0, 0 Lanadelumab: [redacted]	−1,399,767	−2,799,534	−4,899,184	−9,098,485
	Haegarda: 0, 0, 0 Lanadelumab: [redacted]	−2,799,534	−5,599,067	−8,398,601	−16,797,202
Haegarda replaces all Berinert for LTP	Haegarda: [redacted] Lanadelumab: 0, 0, 0	−22,492,000	−22,492,000	−22,492,000	−67,476,001
Haegarda replaces 85% of Berinert LTP[a]	Haegarda: [redacted][b] Lanadelumab: 0, 0, 0	−19,118,200	−19,118,200	−19,118,200	−57,354,601
Haegarda replaces all Berinert SC LTP[a]	Haegarda: [redacted][c] Lanadelumab: 0, 0, 0	−34,103,394	−34,103,394	−34,103,394	−102,310,181
Haegarda replaces 85% of Berinert SC LTP[a]	Haegarda: [redacted][d] Lanadelumab: 0, 0, 0	−25,114,023	−25,114,023	−25,114,023	−75,342,070

BIA = budget impact analysis; IV = intravenous; LTP = long-term prophylaxis; NA: not applicable; SC = subcutaneous.

Note: Negative values denote cost savings.

[a] In this scenario, there is no change to the current proportion of patients using Cinryze ([redacted]%) and no LTP ([redacted]%) in years 1, 2, and 3.

[b] As [redacted]% of patients are using Berinert at baseline, if [redacted]% of patients using Berinert switch to Haegarda, the uptake of Haegarda will be [redacted].

[c] As [redacted]% of patients are using Berinert at baseline, and 75% of those patients are using Berinert SC, in this scenario, if 100% of patients using Berinert SC switch to Haegarda, the uptake of Haegarda will be [redacted].

[d] As [redacted]% of patients are using Berinert at baseline, and 75% of those patients are using Berinert SC, in this scenario, if 85% of patients using Berinert SC switch to Haegarda, the uptake of Haegarda will be [redacted]. The amount of patients continuing to use Berinert LTP is the sum of patients using Berinert for LTP IV [redacted] and those remaining on Berinert SC for LTP [redacted]. In this scenario, we have adjusted Berinert LTP costs by assuming that, of those using Berinert for LTP, 11% are using the SC form (75% × [100% to 85%]) and 89% are using it intravenously.