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Reimbursement Recommendation

Garadacimab (Andembry)

Indication: Routine prevention of attacks of hereditary angioedema (HAE) in adult and pediatric patients (aged 12 years and older). Garadacimab is not intended for acute treatment of HAE attacks.

Sponsor: CSL Behring Canada Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Andembry?

Canada's Drug Agency (CDA-AMC) recommends that Andembry be reimbursed by public drug plans for routine prevention of episodes (also known as *attacks*) of hereditary angioedema (HAE) in adult and pediatric patients (aged 12 years and older) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Andembry should only be covered for adult and pediatric patients (aged 12 years and older) with HAE according to the criteria used by public drug plans for long-term prophylaxis (LTP) currently reimbursed for the prevention of HAE episodes.

What Are the Conditions for Reimbursement?

In addition to following pre-existing criteria for long-term prophylactic treatments currently reimbursed for the prevention of HAE episodes, Andembry should not be used in combination with other medications for long-term prevention of angioedema. The cost of Andembry does not exceed the drug program cost of treatment with the least costly LTP for HAE.

Why Did CDA-AMC Make This Recommendation?

- One clinical trial demonstrated that Andembry reduced the frequency of HAE episodes and improved patients' health-related quality of life (HRQoL) compared with placebo.
- Andembry is an additional treatment option with an alternative mode of administration for patients living with HAE.
- Based on the CDA-AMC assessment of the health economic evidence, Andembry does not represent good value to the health care system at the public list price. The committee determined that there is not enough evidence to justify a greater cost for Andembry compared to the least costly long-term prophylactic treatment for HAE.
- Based on public list prices, Andembry is estimated to result in approximately $25 million in savings over the next 3 years. Stratified analyses demonstrate that cost savings were due to costs increasing for public drug plans with cost savings offset for Canadian Blood Services (CBS) given the displacement of comparator treatments by Andembry.

Summary

Additional Information

What Is HAE?

HAE is a rare hereditary disorder characterized by recurring episodes of painful and potentially life-threatening swelling of the skin, abdomen, or throat. In Canada, it is estimated that 1 in 50,000 people have HAE.

Unmet Needs in HAE

Patients with HAE identified a need for a treatment that offers alternative modes of administration, is effective in preventing episodes, has fewer side effects, and improves HRQoL.

How Much Does Andembry Cost?

Treatment with Andembry is expected to cost approximately $452,651 per patient in year 1 and $417,206 in subsequent years.

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that garadacimab be reimbursed for routine prevention of episodes of HAE in adult and pediatric patients (aged 12 years and older) only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, multicentre, double-blind, placebo-controlled randomized controlled trial (RCT) (VANGUARD; N = 65) that evaluated the efficacy and safety of once-monthly garadacimab subcutaneous (SC) injection for routine prevention of HAE episodes in adult and pediatric patients aged 12 years and older demonstrated that 6 months of treatment with garadacimab resulted in a clinically meaningful reduction in HAE attacks versus placebo. Garadacimab also clinically significantly reduced the number of episodes requiring on-demand treatment and the number of moderate or severe episodes versus placebo. Results from the VANGUARD study also suggest that patients who were receiving garadacimab experienced improvements in their HRQoL, which was considered clinically meaningful based on the threshold identified in the literature; however, analyses for HRQoL outcomes were exploratory. Results from an open-label extension study suggest that the benefits of garadacimab on HAE episodes were maintained over the 1-year follow-up period.

Patients seek additional treatment options that offer alternative modes of administration, are effective in preventing attacks, have fewer side effects, and improve HRQoL as well as offer treatment option for patients with normal C1 esterase inhibitor (C1-INH) HAE. CDEC concluded that garadacimab does not meet the unmet needs identified by patients when compared to other available long-term prophylactic therapies; however, the evidence is supportive of garadacimab as an additional treatment option with an alternative mode of administration for patients living with HAE.

At the sponsor-submitted price for garadacimab and publicly listed price for berotralstat, lanadelumab, and C1-INHs, garadacimab was more costly than berotralstat and may be more costly than lanadelumab depending on the frequency of dosing for lanadelumab. Given the uncertainty with the comparative clinical evidence, the total drug cost of garadacimab should not exceed the total drug cost of treatments with the least costly long-term HAE prophylactic treatment.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation, renewal, discontinuation, and prescribing		
1. Eligibility for reimbursement of garadacimab should be based on the criteria used by each of the public drug plans for initiation, renewal, discontinuation, and prescribing of LTPs currently	CDEC considered it appropriate to align the reimbursement conditions for garadacimab with current Canadian public drug plan reimbursement criteria for LTPs for the routine prevention of episodes of HAE.	Reimbursement could be both in patients who switch from other LTPs and patients who are using garadacimab as a first-line LTP.

Reimbursement condition	Reason	Implementation guidance
reimbursed for the routine prevention of episodes (also known as *attacks*) of HAE with the addition of condition 2 for prescribing.		
Prescribing		
2. Garadacimab should not be used in combination with other medications used for long-term prophylactic treatment of angioedema (e.g., C1 esterase inhibitors, berotralstat, or lanadelumab).	There is no evidence to determine the effects of garadacimab when used in combination with other long-term prophylactic treatments of angioedema (e.g., C1 esterase inhibitors, berotralstat, or lanadelumab).	Patients on long-term prophylactic treatment will continue to require access to on-demand treatments that are used in the management of acute episodes.
Pricing		
3. Garadacimab should be negotiated so that it does not exceed the drug program cost of treatment with the least costly LTP for HAE.	Given the uncertainty associated with the comparative clinical evidence, there is insufficient evidence to justify a cost premium for garadacimab over the least expensive LTP reimbursed for HAE.	—

C1 = complement 1; HAE = hereditary angioedema; LTP = long-term prophylaxis.

Discussion Points

- **Reconsideration request:** The sponsor requested a reconsideration of the initial draft recommendation to reimburse garadacimab for routine prevention of episodes of HAE in adult and pediatric patients (aged 12 years and older). There were 2 issues outlined by the sponsor in the request for reconsideration that were discussed by CDEC. The sponsor requested that CDEC revise its interpretation of the indirect comparative evidence submitted by the sponsor for garadacimab review. The sponsor also requested that the price condition be revised to a price reduction condition rather than the condition that the price does not exceed the drug program cost of treatment with the least costly long-term prophylactic treatment for HAE.
- **Unmet need:** The clinical expert noted to CDEC that not all patients respond to current treatments, and some patients' HAE may become refractory over time. Some treatments also have adverse events, modes of administration, or costs that are deemed unacceptable by patients. CDEC discussed the need to have access to a range of options, especially treatments that are better tolerated, improve compliance, and are more convenient. CDEC concluded that garadacimab does not meet the unmet needs identified by patients when compared to other available long-term prophylactic therapies; however, the evidence is of garadacimab as an additional treatment option with an alternative mode of administration for patients living with HAE.
- **GRADE assessment**: CDEC discussed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment of selected outcomes from the VANGUARD

study for patients with HAE that concluded with high certainty that treatment with garadacimab would result in a clinically important reduction in the number of HAE episodes and increased probability of remaining episode-free over 6 months of treatment compared to placebo. Moderate certainty evidence showed that garadacimab likely results in a clinically important improvement in HRQoL as measured with the Angioedema Quality of Life (AE-QoL) total score and the increase in the number of patients with a clinically important difference on the AE-QoL total score after 6 months compared to placebo.

- **Comparative efficacy and safety between treatments for LTP**: CDEC discussed that although the network meta-analyses (NMAs) submitted by the sponsor suggested that garadacimab improved outcomes in HAE episode rates and HRQoL compared to selected comparators, the certainty of the improvement was affected by the model used (e.g., fixed-effects versus random-effects models), evidence of unaccounted-for heterogeneity, and a limited evidence base that led to sparse networks in the NMAs. Due to these limitations, results from the NMA did not adequately allow for an accurate estimate of the comparative effectiveness of garadacimab to other prophylactic treatments for HAE.
- **Comparative efficacy and safety between garadacimab and lanadelumab:** CDEC also discussed the matching adjusted indirect comparison (MAIC) submitted by the sponsor that compared garadacimab and lanadelumab and noted the heterogeneity across the included studies regarding study designs and patient characteristics. CDEC also noted the differences between the unadjusted and adjusted population characteristics and sensitivity of the primary analysis to assumptions related to homogeneity.
- **Comparative efficacy between garadacimab and berotralstat:** During the reconsideration meeting, CDEC highlighted that the comparison between garadacimab and berotralstat is based solely on indirect evidence from a sparse NMA. Critical assumptions such as transitivity were not fully satisfied. Differences in baseline episode rates, body mass index, and sex distribution across trials introduced substantial heterogeneity. Although random-effects models revealed very wide credible intervals, fixed-effects models risk overstating precision by ignoring heterogeneity. CDEC acknowledged that point estimates from the NMA consistently favoured garadacimab over berotralstat for reducing time-normalized HAE episodes, and E-values suggest this finding is unlikely to be explained by a single unmeasured confounder. However, given the unresolved heterogeneity, sparse data, and methodological limitations, this evidence should be considered supportive rather than confirmatory. To strengthen confidence in comparative effectiveness, more robust evidence would be required. CDEC also noted that given the uncertainty associated with the comparative clinical evidence, there is insufficient evidence to justify a cost premium for garadacimab over the least expensive long-term prophylactic treatment reimbursed for HAE.

Background

HAE is a rare autosomal-dominant genetic disorder that is characterized by recurrent and unpredictable episodes of nonpruritic subcutaneous or submucosal edema. The most commonly affected areas include

the extremities (peripheral episodes), gastrointestinal tract (abdominal episodes), face and oral cavity, and airway (laryngeal episodes). The episodes can be painful and disfiguring, with significant functional impairment and decreased HRQoL. They can also be life-threatening in the case of laryngeal edema.

In Canada, the estimated prevalence of HAE is typically cited as 1 in 50,000 people. HAE is caused by the deficiency (type I HAE) or dysfunction (type II HAE) of the C1-INH enzyme. The diagnosis is based on a detailed history and confirmatory laboratory diagnostic tests. There may be no notable physical signs between episodes. Although the age of onset with HAE is variable, the majority of patients experience their first episode in childhood or adolescence. However, due to its clinical heterogeneity and rarity, patients with HAE may experience delayed diagnoses and misdiagnoses.

Long-term prophylactic therapies for HAE are ongoing treatments that aim to reduce the frequency and severity of HAE episodes and improve patients' HRQoL. Some therapeutic options are available in Canada for long-term prophylactic treatment; however, there is a need for treatments that are better tolerated, improve compliance, and are more convenient.

Garadacimab is a specific inhibitor of activated factor XII and a fully human recombinant monoclonal antibody that binds to the catalytic domain of activated factor XII and inhibits its activity. This ultimately leads to a decrease in bradykinin, the actual mediator of the angioedema in most types of HAE. Garadacimab is indicated for routine prevention of episodes of HAE in adult and pediatric patients (aged 12 years and older). The recommended dosage of garadacimab is an initial loading dose of 400 mg administered subcutaneously as two 200 mg injections on the first day of treatment followed by a monthly dose of 200 mg. Garadacimab is not intended for acute treatment of HAE episodes.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 multicentre, double-blind, placebo-controlled RCT designed to evaluate the efficacy and safety of once-monthly garadacimab SC injection for routine prevention of HAE episodes in adult and pediatric patients aged 12 years and older; 1 long-term extension study; and 2 indirect treatment comparisons (ITCs)
- patients' perspectives gathered by 1 patient group, Hereditary Angioedema Canada (HAE Canada)
- input from public drug plans that participate in the reimbursement review process
- one clinical specialist with expertise diagnosing and treating patients with HAE
- input from 1 clinician group, The Canadian Hereditary Angioedema Network (CHAEN)
- a review of the pharmacoeconomic model and report submitted by the sponsor
- information submitted as part of the sponsor's request for reconsideration (described subsequently)
- feedback on the draft recommendation.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

CDA-AMC received 1 submission from HAE Canada. HAE Canada gathered information from a national survey of 65 respondents as well as a survey of 14 patients who enrolled in the VANGUARD study.

According to the patient input, HAE has a significant impact on patients' and their families' daily lives. Patients reported that they live in fear of unpredictable and debilitating episodes, especially laryngeal episodes. Additional concerns they highlighted pertained to the pain associated with the episodes and the possibility of passing the disease on to their children due to its hereditary nature. Patients also noted other issues, such as having difficulties related to pursuing a career or advanced education, as well as maintaining personal, social, and financial well-being. Unmet needs with currently available treatments included heterogeneity in response to treatment, limited options for LTP, inconvenience of IV treatment or plasma-derived products, lack of access for patients who live in rural areas, and supply interruptions and shortages. The patient input emphasized the following as relevant outcomes: improving control of episodes, convenience and ease of use, as well as reduction of anxiety and fear which affect a patient's ability to work, pursue education, travel, exercise, do household chores, and socialize with family and friends.

Clinician Input

Input From the Clinical Expert Consulted for This Review

HAE is a rare disease involving multiple pathways with highly variable severity and episodes typically recur throughout a person's life. The clinical expert emphasized that a shared decision-making process between patient and specialist physician is the cornerstone in the treatment of HAE, with treatment tailored to the patient's specific needs and goals. These include reducing the frequency and severity of episodes, minimizing side effects, improving quality of life, increasing the ability to maintain employment and education, and maintaining independence. Patients with frequent or severe episodes, or those whose lives are most impacted by their symptoms regardless of frequency and severity, are most in need of treatment. The clinical expert noted that HAE has been associated with a 30% mortality rate due to laryngeal events and emphasized the need to have access to a range of options, especially treatments that are better tolerated, improve compliance, and are more convenient.

Garadacimab is indicated for long-term prevention of HAE events and would fit into the treatment paradigm as an additional option alongside currently used treatments. In some patients who have severe episodes that interfere substantially with their life, LTP can be initiated very early in the course of the disease, and as early as after the first episode. Response to treatment is generally determined by a reduction in the number and severity of episodes, which is expected to result in improved ability for patients to perform activities of daily living. The clinical expert mentioned that patients' expectations may vary because some patients have a target of complete or near complete freedom from all episodes, whereas others may be satisfied with treatment if their episode frequency was reduced by half or even less. Due to the rare nature of HAE, patient's referral to a specialized physician with experience in treating patients with the condition is essential.

According to the clinical expert consulted by CDA-AMC, because the frequency and severity of episodes can vary over time in any patient, and because the condition is lifelong, discontinuing any treatment successfully can be challenging. In addition, there are concomitant factors that may result in a temporary worsening of the disease and loss of response, including surgeries, infections, or stress. For these patients, the expert suggested allowing additional time for response assessment before discontinuing garadacimab.

Clinician Group Input

CDA-AMC received 1 input from CHAEN. Information for this input was gathered from 9 clinicians with experience in treating patients with HAE.

CHAEN noted that "the ultimate goal for an HAE treatment is to achieve no angioedema attacks, and to achieve total control of the disease and normalize the patient's life." According to the input, needs unmet by currently available treatments include the lack of early and sustained prophylactic efficacy, inconvenient methods of administration, tolerability issues (including damage to the veins), and risk of infectious agent transmission through plasma-derived HAE treatments. CHAEN indicated that garadacimab is expected to have a reduced burden compared to infused plasma-derived C1-INH because it is not plasma-derived and is administered subcutaneously once monthly, which can be performed at home. The input noted that garadacimab should be considered along with other currently available treatments for LTP, with patient preference contributing to the ultimate treatment choice. Response to treatment would typically be determined by the number and severity of episodes, requirement for on-demand acute therapy, emergency department visits, hospitalization, and adverse events. Discontinuation of treatment would be based on the absence of effectiveness and toxicities of the treatment.

Drug Program Input

Input was obtained from the drug programs that participate in the reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a recommendation for garadacimab:

- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- system and economic issues.

The clinical expert consulted for the review provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
The pivotal trial (VANGUARD) was placebo controlled. Placebo may not be an appropriate comparator, given the number of therapies available for LTP of HAE, including: • C1 esterase inhibitor (C1-INH) • lanadelumab (Takhzyro) • berotralstat (Orladeyo).	This was a comment from the drug programs to inform CDEC deliberations. CDEC noted that placebo is not an appropriate comparator and that long-term prophylactic treatments of HAE are more appropriate comparators.
Considerations for initiation of therapy	
Inclusion criteria for the VANGUARD trial were as follows: • Patients > 12 years of age with clinically confirmed C1-INH HAE; and • Having > 3 attacks during the 3 months before screening. (If currently on a LTP HAE therapy, ≥ 3 HAE attacks documented over the 3 consecutive months before commencing LTP therapy.) Reimbursement criteria for the other LTP therapies (i.e., lanadelumab, berotralstat) include > 3 HAE attacks within any 4-week period before initiating LTP therapy (that require the use of an acute injectable treatment). Should the initiation criteria for garadacimab align with that of the other LTP therapies (i.e., > 3 HAE attacks within any 4-week period)?	The clinical expert disagreed with the use of a prespecified number of episodes as a requirement to initiate LTP. This is due to variability in disease presentation. Some patients may have fewer episodes in the prespecified time frame, but these episodes could be sufficiently severe to interfere substantially with their life and warrant treatment (e.g., laryngeal episode). Therefore, the expert considered that the decision to initiate LTP should be decided between patients and treating physicians. CDEC recommended that the initiation criteria for garadacimab be aligned with that of other LTPs (i.e., lanadelumab, berotralstat), and that patients must have > 3 HAE events within any 4-week period before initiating long-term HAE prophylactic therapy.
Should patients who experience more severe but less frequent attacks be eligible for coverage?	The clinical expert highlighted that it is very important for patients who experience more severe or more disruptive, but less frequent, episodes be eligible for coverage. CDEC recommended that the initiation criteria for garadacimab be aligned with that of other long-term HAE prophylactic therapies (i.e., lanadelumab, berotralstat), which rely on the number of HAE episodes before initiating treatment.
What is the place in therapy for garadacimab vs. the other LTP therapies for HAE?	The clinical expert considered this still to be determined, but that garadacimab is likely to share a similar target population as lanadelumab. According to the expert, this would likely include FXII-HAE, and any other form of HAE that involves the kallikrein-kinin pathway. CDEC agreed with the clinical expert in that the place in therapy for garadacimab is similar to that of other long-term HAE prophylactic therapies (i.e., lanadelumab, berotralstat). However, CDEC noted there is limited evidence on the efficacy and safety of garadacimab in patients who have FXII-HAE and any other form of HAE that involves the kallikrein-kinin pathway. Therefore, the clinical expert recommended aligning the reimbursement criteria with that of lanadelumab, which limits the reimbursement to patients diagnosed with C1-INH HAE type I and C1-INH HAE type II.
If treatment with garadacimab fails to achieve appropriate response, should patients try another LTP?	CDEC and the clinical expert agreed that patients should try another LTP if garadacimab fails to achieve appropriate response.

Implementation issues	Response
Should patients switch back to comparators after treatment fail to achieve appropriate response?	The clinical expert noted to CDEC that this would depend on how well patients were responding to the original treatment before switching and what factors motivated the switch (e.g., for financial reasons). This would be individualized on a case-by-case basis.
The indication under review at Health Canada does not specify HAE type (i.e., type I, type II, or type III with normal C1-INH levels and activity). The VANGUARD trial only included patients with type I or type II HAE. • Is there any evidence to support the use of garadacimab in type III HAE? • Should patients who have type III HAE be eligible for coverage?	The clinical expert mentioned anecdotal evidence suggesting that garadacimab may be effective in FXII-HAE, but perhaps not in HAE types that do not involve the kallikrein-kinin pathway. The expert considered that, theoretically, drugs would be expected to work in these patients (those who have FXII-HAE). Therefore, the expert suggested that consideration for their use be determined on a case-by-case basis. CDEC noted there is limited evidence on the efficacy and safety of garadacimab in patients who have FXII-HAE, and therefore recommended aligning the reimbursement criteria with that of lanadelumab, which limits the reimbursement to patients diagnosed with C1-INH HAE type I and C1-INH HAE type II.
The initiation criteria for lanadelumab are as follows: • The patient is at least 12 years of age. • The diagnosis of HAE type I or II is made by a specialist physician who has experience in the diagnosis of HAE. • The patient has experienced at least 3 HAE attacks within any 4-week period before initiating lanadelumab therapy that required the use of an acute injectable treatment. Should the initiation criteria for garadacimab be aligned with the initiation criteria for other LTP therapies for HAE (i.e., lanadelumab, berotralstat)?	The criterion regarding prior episodes has been previously addressed. The clinical expert considered that the age and diagnosis criteria were appropriate and should be aligned. However, the expert noted a preference for not systematically excluding patients younger than 12 years if they are symptomatic and if the treating physician deems that LTP is required. CDEC noted there is no evidence in people younger than 12 years and thus no rationale to provide an advantage to garadacimab over comparators. Therefore, CDEC recommended that the initiation criteria for garadacimab be aligned with that of other long-term HAE prophylactic therapies (i.e., lanadelumab, berotralstat) and be initiated in patients who are at least 12 years of age.
Considerations for continuation or renewal of therapy	
How is therapeutic response determined? Is it by the acute use of Firazyr (icatibant injection)? Number of attacks? A 50% reduction in number of HAE attacks like berotralstat?	The clinical expert indicated that all the mentioned response measurements can be considered reasonable and helpful because patients have wide variation in disease in terms of number and severity of episodes and requirements for on-demand rescue medication. CDEC recommended the renewal criteria for garadacimab be aligned with that of other LTPs (i.e., lanadelumab, berotralstat), which rely on the number of HAE episodes before initiating therapy because there is no reason to apply different renewal criteria for garadacimab.
The renewal criteria for lanadelumab are as follows: • An assessment of a response to treatment should be conducted 3 months after initiating treatment with lanadelumab. • A response to treatment is defined as a reduction in the number of HAE attacks for which acute injectable treatment was received within the initial 3 months of treatment with lanadelumab compared to the rate	The clinical expert noted that the renewal criteria can be burdensome and that, ideally, renewal should be determined on a case-by-case basis. However, the expert considered them reasonable and that garadacimab could therefore be aligned with the other long-term prophylaxis therapies regarding renewal. CDEC recommended that the renewal criteria for garadacimab be aligned with that of lanadelumab, including time frame for assessments and definition of response to treatment.

Implementation issues	Response
of attacks observed before initiating treatment with lanadelumab. • Following the initial 3-month assessment, patients should be assessed for continued response to lanadelumab every 6 months. • Continued response is defined as no increase in the number of HAE attacks for which acute injectable treatment was received compared with the number of attacks observed before initiating treatment with lanadelumab. Should the renewal criteria for garadacimab be aligned with the renewal criteria for other LTP therapies for HAE (including time frame for assessments; definition for response to treatment)?	
Considerations for discontinuation of therapy	
The discontinuation criteria for lanadelumab are as follows: • Treatment with lanadelumab should be discontinued in patients who either respond inadequately or exhibit a loss of response, defined as follows: ◦ Inadequate response: No reduction in the number of HAE attacks for which acute injectable treatment was received during the first 3 months of treatment with lanadelumab. ◦ Loss of response: An increase in the observed number of HAE attacks for which acute injectable treatment was received before initiating treatment with lanadelumab. Should the discontinuation criteria for garadacimab be aligned with the discontinuation criteria for other LTP therapies for HAE (including definitions of inadequate response, and loss of response)?	The clinical expert suggested that discontinuation be considered, rather than required, based on these criteria. The expert highlighted that concomitant factors, such as surgeries, infections, or stress, may result in a temporary worsening of the disease and loss of response. For these patients, the expert suggested allowing additional time for response assessment before discontinuing garadacimab. CDEC recommended that the discontinuation criteria for garadacimab be aligned with that of lanadelumab, including definitions of inadequate response and loss of response.
Considerations for prescribing of therapy	
Is there any evidence to support the use of garadacimab in combination with other LTP therapies for HAE?	The clinical expert noted that there is no such evidence, but that long-term prophylactic therapies are sometimes used in combination in clinical practice, appropriately or not. CDEC recommended that garadacimab should not be used in combination with other medications used for long-term prophylactic treatment of angioedema (e.g., C1-INHs, berotralstat, or lanadelumab).
The prescribing criteria for lanadelumab are as follows: • The patient must be under the care of a specialist experienced in the diagnosis and management of patients with angioedema. • Lanadelumab should not be used in combination with other medications used for long-term prophylactic treatment of angioedema (e.g., C1-INH). • The dose of lanadelumab should not be escalated to more than 300 mg every 2 weeks (q.2.w.) in cases of	The clinical expert agreed with the first criterion regarding receiving specialist care. The expert indicated that the combination of long-term prophylactic treatments is a topic of interest in clinical practice and that although some patients may eventually benefit from this, it is generally discouraged. As indicated previously, there is currently no evidence in that regard. The expert also noted that in exceptional circumstances, the dosage of garadacimab could be escalated beyond the

Implementation issues	Response
inadequate response or loss of response. Should the prescribing criteria for garadacimab be aligned with the prescribing criteria for other LTP therapies for HAE (including being under the care of a specialist experienced in the diagnosis and management of patients with angioedema; maximum reimbursed dose in cases of inadequate response or loss of response; and so on)?	recommended dose if there is inadequate response. CDEC recommended that the prescribing criteria for garadacimab be aligned with that of lanadelumab, including receiving care from a specialist experienced in the diagnosis and management of patients with angioedema and not using in combination with other medications used for long-term prophylactic treatment of angioedema. CDEC also noted that there is no evidence to support the use of higher doses, and that the dosage should follow the Health Canada–recommended dosage of garadacimab, which is an initial loading dose of 400 mg administered subcutaneously as two 200 mg injections on the first day of treatment followed by a monthly dose of 200 mg.
Generalizability	
When should patients switch from comparator (i.e., lanadelumab or berotralstat) to garadacimab?	CDEC and the clinical expert agreed that reasons for switching to garadacimab could include lack of efficacy, toxicity, mode of administration, and coverage issues with comparators.
System and economic issues	
• Plasma-derived products are funded through CBS whereas non–plasma-based products are reimbursed through the drug plans. • Products accessed through CBS maybe be available to patients at no cost; whereas, products accessed through the drug plans may be subject to deductibles and/or copays. • Patients transitioning from plasma-derived products to garadacimab may result in cost shifting within the system — from CBS to the drug programs.	This was a comment from the drug programs to inform CDEC deliberations.
• Lanadelumab has successfully completed pCPA negotiations and has a confidential negotiated price. • Berotralstat is currently under active negotiations at pCPA. • Plasma-derived products are procured through purchase agreements through CBS.	This was a comment from the drug programs to inform CDEC deliberations.

C1-INH = C1 esterase inhibitor; CBS = Canadian Blood Services; CDEC = Canadian Drug Expert Committee; FXII = factor XII; FXII-HAE = HAE with *FXII* mutations; HAE = hereditary angioedema; LTP = long-term prophylaxis; pCPA = pan-Canadian Pharmaceutical Alliance.

Clinical Evidence

Systematic Review

Description of Studies

One study was reviewed: VANGUARD (N = 65) was a phase III, multicentre, double-blind, placebo-controlled RCT designed to evaluate the efficacy and safety of once-monthly garadacimab SC injection for routine prevention of HAE episodes in adult and pediatric patients aged 12 years and older. On-demand HAE

therapies were permitted at any time during the study for the treatment of HAE episodes and were received by patients in both treatment groups.

The primary outcome in the study was the time-normalized number of HAE episodes over 6 months. Each individual HAE episode had to be associated with at least 1 symptom or location. HAE symptoms could develop concurrently or consecutively. *Episode resolution* was defined as no longer having symptoms of a potential episode for a minimum of 24 hours. Investigator-reported HAE episodes were based on a review of patients' self-reported HAE symptoms, interference with daily activities, and use of on-demand medication to treat those symptoms. Patients were to be trained by the site's personnel on identifying symptoms of a potential HAE episode and were asked to notify and report details to the study site within 72 hours of the start of the first symptom. Additional outcomes related to HAE episodes were assessed as secondary outcomes in the trial and included change from baseline in the frequency of HAE episodes, episodes requiring on-demand treatment, and moderate and/or severe episodes.

HRQoL was an exploratory outcome in the study and was assessed at 6 months using the AE-QoL questionnaire. The AE-QoL questionnaire is a patient-reported disease-specific measure to assess quality of life impairment in patients with recurrent angioedema episodes. The questionnaire covers 4 domains (functioning, fatigue or mood, fears or shame, and nutrition). Responses range from never to very often. The total score and individual domain scores are generated and converted to a linear scale of 1 to 100, with higher scores representing higher impairment.

Efficacy Results

HAE Episodes

Outcomes related to HAE episodes were considered appropriate by the clinical expert because reducing the frequency and severity of episodes is one of the main treatment goals in HAE. In addition, these were consistent with the patient and clinician input, highlighting the importance of better control of HAE episodes, including a reduction in the number and severity of episodes and requirement for on-demand acute therapy.

In patients with type I and type II HAE, the use of garadacimab was associated with a mean difference between groups in the time-normalized number of HAE events reported per patient per month of −1.74 events (95% confidence interval [CI], −2.34 to −1.13 events; $P < 0.001$) over 6 months versus placebo. For absolute effect, a total of 63 HAE events were reported throughout the treatment period in the 39 patients who received garadacimab, while 264 HAE events were reported in the 25 patients who received placebo. Results from sensitivity analyses were supportive of the primary analysis. Therefore, treatment with garadacimab results in a clinically important reduction in the number of HAE events compared to placebo.

Similarly, the use of garadacimab was associated with a clinically important reduction in the number of HAE events requiring on-demand treatment (mean difference between groups per patient per month = −1.63 events; 95% CI, −2.26 to −1.00 events; $P < 0.001$), and in the number of moderate or severe HAE events (mean difference between groups per patient per month = −1.23 events; 95% CI, −1.73 to −0.73 events; $P < 0.001$) over 6 months versus placebo.

HAE events were also assessed as a reduction from baseline in the number HAE events over 6 months of treatment with garadacimab compared to the number observed with treatment with placebo. The run-in period was relatively short to determine the baseline rate of events because of the unpredictable nature of HAE episodes which introduced uncertainty surrounding the findings. Garadacimab likely resulted in a clinically important reduction in the number of HAE events, with a between-group difference of 70.46% (95% CI, 51.25% to 89.67%; P < 0.001).

Finally, treatment with garadacimab resulted in a clinically important increase in the proportions of patients who remained episode-free over 6 months versus placebo, an outcome which was not affected by the variability in the baseline episode rate. Throughout the treatment period, 24 (61.5%) of 39 patients in the garadacimab group remained episode-free, while none of the 25 patients in the placebo group remained episode-free, resulting in a between-group difference of 61.54% (95% CI, 46.27% to 76.81%; P < 0.001).

AE-QoL Questionnaire

Treatment with garadacimab likely results in a clinically important improvement in HRQoL as measured with the AE-QoL total score over 6 months compared to placebo (mean between-group difference = −24.265 points; 95% CI, −34.976 to −13.554 points). In addition, the proportion of patients with a clinically important improvement of 6 points on the AE-QoL total score over 6 months was 87.9% (29 of 39 patients) in the garadacimab group and 55.0% (11 of 25 patients) in the placebo group. However, uncertainty was introduced in the assessment of HRQoL because the run-in period was relatively short to determine the baseline rate of episodes due to the unpredictable nature of HAE episodes. Therefore, these findings were likely to be clinically important, based on thresholds identified in the literature.

Harms Results

A total of 64% of patients receiving garadacimab and 60% of patients receiving placebo reported at least 1 adverse event. The most common treatment-emergent adverse events were related to infections, gastrointestinal disorders, and injection site reactions. One patient who was receiving garadacimab reported a serious adverse event of HAE that included a laryngeal episode. No patients who received placebo experienced a serious adverse event. Treatment with garadacimab appeared to be well tolerated because there were no withdrawals due to adverse events. No deaths were reported in the study. Adverse events of special interest included thromboembolic events, bleeding events, and severe hypersensitivity or anaphylaxis. The sponsor reported that none of the patients assessed experienced any of these events during the trial. The clinical expert indicated that the overall harms profile of garadacimab in the VANGUARD study did not raise any particular safety signals.

Critical Appraisal

The VANGUARD study used a relatively short run-in period to determine the baseline rate of episodes due to the unpredictable nature of HAE episodes, which are not necessarily consistent throughout a patient's life. As a result, there is uncertainty surrounding the baseline episode rate. However, variability in the baseline episode rate would only impact the interpretation of the analyses based on the change from the baseline. On-demand therapies were permitted at any time during the study for the treatment of HAE episodes, but routine long-term prophylaxis therapies were prohibited. Although there were no obvious differences between

groups, prior and concomitant medications were reported together, so it is not possible to assess with certainty that there were no important differences in the concomitant drugs received. These could change the magnitude of response to current treatment, according to the clinical expert, because some therapies are expected to have a longer-lasting protective effect than others. Because the VANGUARD study included a placebo control group, there is no direct evidence comparing garadacimab to other long-term prophylactic therapies. The clinical meaningfulness of the overall number of episodes, the number of moderate or severe episodes, and the number of episodes requiring on-demand treatment can be highly variable across patients depending on how these impact their daily lives because different individuals will have different priorities and objectives when assessing their magnitude of response to treatments.

Findings from the VANGUARD study can be considered generalizable to patients with type I or II HAE living in Canada because baseline patient characteristics, disease history, and use of HAE on-demand acute therapies were considered representative of the population routinely seen in clinical practice. Patients in the study had a baseline episode rate of at least 2 episodes per month, which the clinical expert stated may be higher than the typical frequency at which LTP is initiated in clinical practice. At the other end of the spectrum, the trial only included patients considered medically appropriate for on-demand treatment as the sole management of their HAE and may not have included patients with more severe HAE who could not tolerate discontinuation of their current long-term prophylactic therapy. There were few adolescents enrolled in the VANGUARD study; therefore, there are limited data to interpret in this younger age group. The follow-up duration of 6 months was considered sufficient but relatively short to capture a change in HAE episode occurrence because the disease may be highly variable. Although long-term prophylactic therapy is potentially lifelong, evidence is limited beyond the study follow-up duration.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null.

Table 3 presents the GRADE summary of findings for garadacimab versus placebo.

The selection of outcomes for the GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with a clinical expert, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- number of HAE events during the treatment period
- reduction in event rate during the treatment period compared to the run-in period
- HRQoL (AE-QoL questionnaire).

Table 3: Summary of Findings for Garadacimab vs. Placebo for Prevention of Events in Patients With HAE

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects			Certainty	What happens
			Placebo	New drug	Difference		
Number of HAE episodes							
Time-normalized number of HAE episodes per month during the treatment period Follow-up: 6 months	Garadacimab: n = 39 Placebo: n = 25 (1 RCT)	NR	Observed mean (per month): 2.01 events (SD = 1.341)	Observed mean (per month): 0.27 events (SD = 0.683)	Mean difference between groups = −1.74 events (95% CI, −2.34 to −1.13)	High[a]	Garadacimab results in a clinically important reduction in the number of HAE events over 6 months compared to placebo.
Reduction in HAE episode rate							
Reduction in time-normalized number of HAE episodes per month during the treatment period compared to the run-in period Follow-up: 6 months	Garadacimab: n = 39 Placebo: n = 25 (1 RCT)	NR	Observed mean = 20.21% (SD = 42.661%)	Observed mean = 90.67% (SD = 22.433%)	Mean difference between groups = 70.46% (95% CI, 51.25% to 89.67%)	Moderate[b]	Garadacimab likely results in a clinically important reduction from baseline in the number HAE events over 6 months compared to that observed with placebo.
Number of patients who had a 100% reduction in the number of HAE episodes during the treatment period Follow-up: 6 months	Garadacimab: n = 39 Placebo: n = 25 (1 RCT)	Mean difference between groups = 61.54 (46.27 to 76.81)	0 per 1,000 patients	615 per 1,000 patients	615 more per 1,000 patients	High[c]	Garadacimab results in a clinically important increase in the probability of being episode-free over 6 months compared to placebo.
HRQoL							
Change from baseline in AE-QoL total score Follow-up: 6 months	Garadacimab: n = 33 Placebo: n = 20 (1 RCT)	NR	Observed mean = −2.206 (SD = 19.1296)	Observed mean = −26.471 (SD = 17.8943)	Mean difference between groups = −24.265 (95% CI, −34.976 to −13.554)	Moderate[d]	Garadacimab likely results in a clinically important improvement in HRQoL as measured with the AE-QoL total score at 6 months compared to placebo.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects			Certainty	What happens
			Placebo	New drug	Difference		
Proportion of patients with MCID in AE-QoL total score during the treatment period Follow-up: 6 months	Garadacimab: n = 33 Placebo: n = 20 (1 RCT)	NR	744 per 1,000 patients	440 per 1,000 patients	304 fewer per 1,000 patients	Moderate[d]	Garadacimab likely results in a clinically important increase in the number of patients who achieve a clinically important difference on the AE-QoL total score over 6 months compared to placebo.
Harms							
Patients with serious adverse events Follow-up: 6 months	Garadacimab: n = 39 Placebo: n = 25 (1 RCT)	NR	0 per 1,000 patients	25 per 1,000 patients	25 more per 1,000 patients	Low[e]	The evidence is uncertain about the effect of garadacimab on serious adverse events over 6 months compared to placebo.

AE-QoL = Angioedema Quality of Life; CI = confidence interval; HAE = hereditary angioedema; MCID = minimal clinically important difference; NR = not reported; RCT = randomized controlled trial.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a]The presence of an important effect was based on a threshold of at least 1 time-normalized episode per month as a difference between groups, which was informed by the clinical expert consulted for this review.

[b]Rated down 1 level for study limitation because the VANGUARD study used a relatively short run-in period to determine the baseline rate of episodes. Given the unpredictable nature of HAE episodes, this limited observation time adds uncertainty to the baseline rate and impacts the interpretation of the analyses based on the change from baseline. The presence of an important effect was informed by the clinical expert consulted for this review.

[c]Not rated down because the variability in the baseline episode rate would not affect the interpretation of this outcome, which was based on the between-group difference in absence of on-treatment episodes. The presence of an important effect was informed by the clinical expert consulted for this review.

[d]Rated down 1 level for study limitation because the VANGUARD study used a relatively short run-in period to determine the baseline rate of episodes. Given the unpredictable nature of HAE episodes, this limited observation time adds uncertainty to the baseline rate and impacts the interpretation of the analyses based on the change from baseline. Statistical testing for HRQoL outcomes did not adjust for multiplicity in the trial and should be considered as supportive evidence. The presence of an important effect was based on a threshold of 6 points identified in the literature.

[e]Rated down 2 levels because of the low number of events in the study and the absence of statistical comparison between treatment groups.

Source: CSL312_3001 (VANGUARD study) Clinical Study Report and the sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

Description of Studies

One long-term extension study was reviewed and summarized. Study CSL312_3002 is an ongoing multicentre, open-label, phase IIIb study designed to investigate the clinical safety and efficacy of SC administered garadacimab in the prophylactic treatment of HAE when administered monthly for at least 12 months. The primary objective of the study was to evaluate the long-term safety of SC administration of garadacimab in the prophylactic treatment of patients with C1-INH HAE. The secondary objectives were to evaluate long-term efficacy, including patient-reported assessment of response to therapy. Patients enrolled in this study were patients who successfully completed the VANGUARD study, patients who successfully completed Study CSL312_2001 (phase II study not summarized in this review), and patients with no prior exposure to garadacimab. A total of 161 patients entered the open-label extension study, including 35 patients who rolled over from the phase II study, Study CSL312_2001 (2 had HAE with *FXII* mutations [FXII-HAE]), 57 patients were rolled over from the VANGUARD trial, and 69 patients had not previously participated in a garadacimab study.

Efficacy Results

The mean time-normalized number of HAE events per month for all patients and for patients who continued garadacimab from VANGUARD trial were 0.16 events (SD = 0.370 events) and 0.11 events (SD = 0.316 events), respectively. The mean reduction in the time-normalized number of HAE events during the treatment period compared to the run-in period was 94.67% (SD = 11.983%) in all patients screened and assigned to treatment (treated analysis set) and 96.15% (SD = 9.019%) in patients who continued garadacimab from the VANGUARD trial. A total of 59.6% of patients did not experience any episodes at the data cut-off date of February 13, 2023; the median duration of the efficacy evaluation period in these patients was 13.83 months (range, 3.0 to 21.1 months). The mean time-normalized number of HAE events requiring on-demand treatment per month during the treatment period for the treated analysis set and for those who continued garadacimab from the VANGUARD study was 0.14 events (SD = 0.358 events) and 0.10 events (SD = 0.316 events), respectively. For the treated analysis set, the mean time-normalized number of moderate or severe HAE events per month during the treatment period was 0.11 events (SD = 0.277 events), and the time-normalized number of moderate or severe events requiring on-demand treatment per month during the treatment period was 0.11 events (SD = 0.274 events). The least squares mean for change from baseline to 12 months in the AE-QoL score was 33.337 points (standard error [SE] = 1.725 points; 95% CI, −36.7725 to −29.9023 points) in patients with no prior exposure to garadacimab and −2.745 points (SE = 1.510 points; 95% CI, −5.7623 to 0.2718) in patients with prior exposure to garadacimab.

Harms Results

Overall, 135 (83.9%) of 161 patients experienced treatment-emergent adverse events. The most frequently reported treatment-emergent adverse events (occurring in ≥ 5% of patients) were COVID-19 (36.0%), nasopharyngitis (16.8%), injection site erythema (6.8%), influenza (6.8%), headache (6.2%), and upper respiratory tract infection (5.6%). No patients were assessed by the investigator as experiencing adverse events of special interest as per the protocol; however, adverse events of special interest as identified

by Standardized MedDRA Query included bleeding events (n = 10) and severe hypersensitivity including anaphylaxis (n = 26). A total of 3 patients reported serious adverse events (2 cases of COVID-19 and 1 HAE event). Treatment with garadacimab was discontinued in 2 patients due to treatment-emergent adverse events of injection site irritation (moderate) and mood swings (severe). No deaths were reported.

Critical Appraisal

This open-label study is still ongoing; 3 patients completed the study, and 119 patients had at least 12 months of exposure at the data cut-off of February 13, 2023. The lack of a control group precludes causal statements about benefit and harm compared with any comparator. The open-label nature of the study increases the risk of bias in determining the magnitude of the safety outcomes and efficacy end points that include subjective assessments because the lack of blinding may affect patients' expectations of treatment and investigators' assessments. The direction and magnitude of this potential bias remain unclear. This study included 71 patients who were previously treated with garadacimab and were rolled over from the parent trials. It is possible that patients who continued and remained on the treatment were also those whose HAE responded well to the drug. This may increase the risk of selection bias. There was no imputation of missing values in this trial; however, the attrition rate at the cut-off date was 6.8%; as a result, the risk of bias due to missing data is not considered high.

Patients who were pregnant or breastfeeding or who had concomitant conditions, such as another form of angioedema, recurrent angioedema associated with urticaria, clinically significant bleeding due to coagulopathy, thrombotic disorder, significant illnesses, or major comorbidities, were not included in this study; therefore, the results are not generalizable to these subpopulations. The study included 10 adolescent patients. Because of the small sample size, it is unlikely that the results would be broadly generalizable to all adolescent patients with HAE. In this trial, the maximum allowed dosage for patients with C1-INH HAE was 400 mg per month and the maximum allowed dosage for the 2 patients with normal C1-INH *FXII* mutation was 600 mg per month. These values were all higher than the recommended dosage in the product monograph, which recommends an initial loading dose of 400 mg administered subcutaneously as two 200 mg injections on the first day of treatment followed by a monthly dose of 200 mg.

Indirect Comparisons

Description of Studies

Due to the lack of direct evidence comparing garadacimab with other existing therapies for routine prevention of episodes of HAE in adult and pediatric patients (aged 12 years and older), the sponsor conducted 2 ITCs, including an NMA of several long-term prophylactic treatments and a separate MAIC between garadacimab and lanadelumab.

Efficacy Results

The NMA results suggested that treatment with garadacimab improved outcomes compared with selected comparators but the confidence in the results varied based on the model used. The random-effects models, which were likely more appropriate for capturing between-study heterogeneity, produced wider 95% credible

intervals that overlapped unity in contrast to the narrower credible intervals observed with the primary fixed-effects models.

The MAIC results also suggested that treatment with garadacimab improved efficacy compared with lanadelumab (both administered every 2 weeks and every 4 weeks). The results varied widely depending on the model used (e.g., unadjusted or adjusted) and sensitivity analyses suggested the models were sensitive to the studies included.

Harms Results

In the NMA, the proportion of patients with treatment-emergent adverse events with garadacimab 200 mg once monthly was numerically higher compared with C1-INH concentrate (Haegarda) 60 mg twice weekly, but numerically lower compared with berotralstat (Orladeyo) 150 mg once daily, lanadelumab (Takhzyro) 300 mg every 4 weeks, and lanadelumab (Takhzyro) 300 mg every 2 weeks. No statistically significantly difference was observed. In the MAIC, safety outcomes were not assessed.

Critical Appraisal

Overall, the ITCs (NMA and MAICs) were conducted according to accepted methodological guidance. The potential key limitation of the NMA was the heterogeneity (in effect modifiers and prognostic factors) across the included studies in terms of the study designs and patient characteristics. Other potential limitations included that all evidence networks were sparse, and the connections between treatment nodes were typically informed by only a single trial, the sample sizes of the included studies were relatively small, and the HAE events were relatively rare. Together, all these limitations may increase the potential for biased treatment effect estimates, which limit the robustness of the NMA. Despite reasonable procedures to identify and rank potential and relevant effect modifiers, the potential key limitations of the MAICs included that not all important effect modifiers were able to be matched and adjusted and the HAE event numbers were low. Furthermore, the MAIC method reduces effect sample size (i.e., up to more than 50% reduction). Overall, the results of the NMA and MAICs should be interpreted with consideration of these limitations. This suggests that the assumption of similarity may not hold true for either ITC, increasing the likelihood of bias and uncertainty about the validity of the results for determining the comparative effectiveness of garadacimab.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	For the routine prevention of attacks of hereditary angioedema in adult and pediatric patients aged 12 years and older.
Treatment	Garadacimab
Dose regimen	Loading dose of 400 mg on the first day of treatment followed by a monthly dose of 200 mg
Submitted price	$34,840 per 200 mg single-dose prefilled pen or prefilled syringe
Submitted treatment cost	First year: $452,651 Subsequent years: $417,206
Comparators	• Berotralstat • C1-INH IV • C1-INH SC • Lanadelumab
Perspective	Canadian publicly funded health care payer
Outcomes	Quality-adjusted life-years, life-years
Time horizon	Lifetime (58.8 years)
Key data sources	• Sponsor-submitted NMA informed the comparative efficacy (i.e., proportion of patients in the starting health states and the episode rate) of garadacimab vs. comparators. • Individual trials informed the remaining efficacy and safety parameters that were naively compared within the sponsor's model.
Key limitations	• The comparative efficacy and safety of garadacimab relative to other long-term prophylactic treatments for the routine prevention of episodes of hereditary angioedema is uncertain owing to a lack of direct head-to-head trials and limitations with the sponsor's NMA. Key limitations with the indirect evidence include significant heterogeneity across included trials, a sparse network, relatively small trial size, and wide credible intervals. Together, the NMA results need to be interpreted with caution. In addition, the sponsor's approach to naively combine the remaining efficacy and safety parameters without statistical adjustment introduces significant uncertainty in the comparison against long-term prophylactic treatment. • There is uncertainty to the dosing schedule of lanadelumab. Although the sponsor assumed 20% of patients will switch from the starting dosage of 300 mg every 2 weeks to a dosage of 300 mg every 4 weeks, clinical expert input sought by CDA-AMC noted the proportion of patients switching to 300 mg every 4 weeks dosage is likely higher than 20% and would vary by jurisdiction given their reimbursement criteria for lanadelumab.
CDA-AMC reanalysis results	• CDA-AMC was unable to address uncertainty in the comparative clinical evidence. Although a CDA-AMC base case could not be specified, there is insufficient clinical evidence to justify a price premium for garadacimab relative to currently available long-term prophylactic treatments.

C1 – INH = C1 esterase inhibitor; CDA-AMC = Canada's Drug Agency; ICER = incremental cost-effectiveness ratio; NMA = network meta-analysis; SC = subcutaneous; vs. = versus.

Budget Impact

CDA-AMC identified the following limitations with the sponsor's analysis: the proportion of patients eligible for public coverage was likely underestimated, market shares in the reference scenario may not reflect expected uptake, uncertainty in the treatment episode rates, uncertainty in the proportion of patients receiving lanadelumab who would switch from every 2 weeks to every 4 weeks, and the analysis is based on published list prices. Based on the CDA-AMC reanalysis, the 3-year budget impact to public drug plans of introducing garadacimab for the routine prevention of episodes of HAE in adult and pediatric patients (aged 12 years and older) is expected to result in budget savings of $25,578,097 (budget savings of $5,411,578 in year 1, $8,494,679 in year 2, and $11,671,840 in year 3). Analyses stratified by drug plan demonstrate that the cost savings were due to increased costs for public drug plans associated with garadacimab being less than cost savings for CBS due to the displacement of C1-INH by garadacimab. Uncertainty remains in this estimate because the analyses do not reflect the existing reimbursement criteria of comparator treatments or their confidentially negotiated drug prices, which may result in lower treatment costs for comparator therapies. Uncertainty in the proportion of patients who switch from lanadelumab every 2 weeks to every 4 weeks may further impact the magnitude of budget savings predicted.

Request for Reconsideration

The sponsor filed a request for reconsideration of the draft recommendation for garadacimab be reimbursed for routine prevention of episodes of HAE in adult and pediatric patients (aged 12 years and older). In their request, the sponsor identified the following issues:

- The sponsor requested that CDEC revise its interpretation of the indirect comparative evidence submitted for garadacimab.
- The sponsor requested that the price condition be revised to a price reduction condition rather than the condition that the price does not exceed the drug program cost of treatment with the least costly long-term prophylactic treatment for HAE.

In the meeting to discuss the sponsor's request for reconsideration, CDEC considered the following information:

- information from the initial submission related to the issues identified by the sponsor
- feedback from 1 clinical specialists with expertise in the diagnosing and treating patients with HAE
- feedback on the draft recommendation from 2 patient groups, CHAEN and HAE Canada Inc.
- feedback on the draft recommendation from the public drug plans that participate in the reimbursement review process.

All feedback received in response to the draft recommendation is available on the CDA-AMC website.

CDEC Information

Initial Meeting Date: December 18, 2024

Members of the committee: Dr. Peter Jamieson (Chair), Dr. Sally Bean, Daryl Bell, Dan Dunsky, Dr. Trudy Huyghebaert, Morris Joseph, Dr. Dennis Ko, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Dr. Edward Xie, and Dr. Peter Zed.

Regrets: One expert committee member did not attend.

Conflicts of interest: One expert committee member did not participate due to considerations of conflict of interest.

Reconsideration Meeting Date: December 18, 2025

Members of the committee: Dr. Peter Jamieson (Chair), Dr. Kerry Mansell (Vice-Chair), Sally Bean, Daryl Bell, Dan Dunsky, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Dr. Dennis Ko, Dr. Christine Leong, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Carla Velastegui, Dr. Edward Xie, and Dr. Peter Zed.

Regrets: Three expert committee members did not attend.

Conflicts of interest: None

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Questions or requests for information about this report can be directed to Requests@cda-amc.ca.