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CADTH Reimbursement Recommendation

Berotralstat (Orladeyo)

Indication: For routine prevention of attacks of hereditary angioedema in adults and pediatric patients 12 years of age and older

Sponsor: BioCryst Pharmaceuticals Inc.

Final recommendation: Reimburse with conditions

CADTH

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Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Orladeyo?

CADTH recommends that Orladeyo be reimbursed by public drug plans for routine prevention of attacks of hereditary angioedema (HAE) in adults and pediatric patients 12 years of age and older, if certain conditions are met.

Which Patients Are Eligible for Coverage?

Orladeyo should only be reimbursed for adults and adolescents with HAE according to the criteria used by public drug plans for lanadelumab for the prevention of HAE attacks.

What Are the Conditions for Reimbursement?

In addition to following pre-existing criteria for lanadelumab, Orladeyo should not be used in combination with other medications for long-term prevention of angioedema. Orladeyo should only be reimbursed if its cost is reduced.

Why Did CADTH Make This Recommendation?

- Two clinical trials demonstrated that Orladeyo reduced the frequency of HAE attacks compared with placebo.
- Orladeyo may meet some needs that are important to patients, such as administration by mouth rather than injection, and fewer HAE attacks.
- Based on CADTH's assessment of the health economic evidence, Orladeyo does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Orladeyo is estimated to cost the public drug plans approximately $93 million over the next 3 years. However, the actual budget impact is uncertain given large differences between the sponsor's and CADTH's reported budget impact, and because it includes products provided through both Canadian Blood Services and public drug plans.

Additional Information

What Is HAE?

HAE is a rare hereditary disorder, with which patients experience recurring episodes of painful and potentially life-threatening swelling of the skin, abdomen, or throat. It is estimated that 1 in 93,000 to 1 in 50,000 people have HAE.

Unmet Needs in HAE

Current treatments reimbursed to prevent HAE attacks require injection, and some are made from blood products. Other treatment options are needed that reduce HAE attacks but are easier to administer.

How Much Does Orladeyo Cost?

Treatment with Orladeyo is expected to cost approximately $310,463 per patient annually.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that berotralstat be reimbursed for the routine prevention of attacks of hereditary angioedema (HAE) in adults and pediatric patients 12 years of age and older, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Two double-blind randomized controlled trials (APeX-2 [N = 80] and APeX-J [N = 13]) in patients with type 1 or 2 HAE who had experienced at least 2 confirmed HAE attacks in the 56 days before the start of the trials demonstrated that, compared with placebo, 24-week treatment with berotralstat 150 mg daily was associated with statistically significant and clinically meaningful reduction in the frequency of investigator-confirmed HAE attacks. In the pivotal APeX-2 study, the rate of investigator-confirmed HAE attacks per month was 1.31 for the berotralstat 150 mg daily group and 2.35 for the placebo group during the 24-week double-blind treatment period, with a relative rate reduction of 44.2% (95% CI, 23.0% to 59.5%; P < 0.001) versus placebo. The relative rate reduction in investigator-confirmed HAE attacks was consistent in the supportive APeX-J study (49.1%; 95% CI, 20.4% to 67.5%; P = 0.003). Patients who received berotralstat 150 mg daily reported approximately 13 fewer symptom-days over the 24-week treatment period than those in the placebo group of the APeX-2 study. Also, 58% of patients in the berotralstat 150 mg group, compared with 25% in the placebo group, achieved at least a 50% relative reduction in the rate of investigator-confirmed HAE attacks compared to baseline.

Patients seek additional treatment options that offer a convenient mode of delivery (including for those who have damaged veins), are effective in preventing attacks, have fewer side effects, and improve health-related quality of life (HRQoL). The trials demonstrated that, compared to placebo, some patients may see some of these important unmet needs addressed by berotralstat, including preventing HAE attacks.

Using the sponsor-submitted price for berotralstat, and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for berotralstat was $14,559,490 per quality-adjusted life-year (QALY) compared with no long-term prophylaxis (LTP). A price reduction is required for berotralstat to be considered cost-effective at a $50,000 per QALY threshold.

Table 1: Reimbursement Conditions and Reasons

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

Reimbursement condition	Reason	Implementation guidance
of HAE with the addition of condition 2 for prescribing.		
Prescribing		
2. Berotralstat should not be used in combination with other medications used for LTP treatment of angioedema (e.g., C1-esterase inhibitors or lanadelumab).	There is no evidence to determine the effects of berotralstat when used in combination with other LTP treatment of angioedema (e.g., C1-esterase inhibitors or lanadelumab).	Patients on LTP treatment will continue to require access to on-demand treatments that are used in the management of acute attacks.
Pricing		
3. A reduction in price.	The ICER for berotralstat is $14,559,490 when compared with no LTP. A price reduction of 93% would be required for berotralstat to be able to achieve an ICER of $50,000 per QALY compared to no LTP. The sponsor claims that the funding of berotralstat will result in cost savings to the health care system. There is a lack of direct or indirect comparative evidence vs. other LTP treatments. Further, the relative costs cannot be determined as the cost of the C1 esterase inhibitors is not funded by the public drug plan. Therefore, any estimate on the incremental benefit and cost-effectiveness of berotralstat vs. LTP treatments is unknown. There is no evidence to warrant a price premium for berotralstat over existing LTP treatments funded for prevention of attacks of HAE.	—
Feasibility of adoption		
4. The feasibility of adoption of berotralstat must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimates.	—

C1 = complement 1; HAE = hereditary angioedema; ICER = incremental cost-effectiveness ratio; LTP = long-term prophylaxis; QALY = quality-adjusted life-year.

Discussion Points

- The sponsor requested a reconsideration of the initial draft recommendation to not reimburse berotralstat for routine prevention of attacks of HAE in adults and pediatric patients aged 12 years and older. CDEC discussed each of the issues identified by the sponsor in their request for reconsideration.

- During the initial and reconsideration meetings, CDEC discussed that the control group in the trials received placebo plus acute rescue therapy, which is not consistent with international and Canadian clinical practice guidelines for this patient population, which recommend complement-1 esterase inhibitors (C1-INHs) or lanadelumab as first line treatment options for LTP. In addition, the trial included patients who were medically appropriate for on-demand treatment as the sole management of HAE. Prior to enrolment in the APeX-2 study, participants were required to discontinue LTP therapy and undergo a washout period. As such, an evidence gap exists for the use of berotralstat in patients who are unable or unwilling to discontinue LTP of which 1 potential reason could be disease severity.
- During the reconsideration meetings, CDEC discussed the feedback received on the draft recommendation from the clinician groups regarding the lack of direct or indirect evidence comparing berotralstat to other LTP, and the relevance of placebo plus acute treatment as a comparator. In the reconsideration discussion, the clinical expert consulted by CADTH noted to CDEC that on-demand treatment as the sole management of HAE may still be considered for some patients, and the decision to start LTP is multifactorial, including patient preference. CDEC discussed that there is no commonly accepted threshold for the frequency of HAE attacks that would warrant initiating LTP therapy. The mean baseline attack rate of patients in the APeX-2 study was 3 within a 4-week period, which, according to the clinical expert consulted by CADTH, is consistent with the attack rate of patients likely to initiate LTP therapy in clinical practice.
- CDEC noted that an evidence gap remains on the comparative efficacy and safety of berotralstat versus other LTP options available in Canada, and that it would be feasible to conduct an active controlled trial to address this gap and collect real-world evidence on the use of the drug in the Canadian population.
- Although patients expressed the desire for an option that is easier to administer, it is uncertain whether oral berotralstat would provide similar clinical efficacy compared to currently available treatments that are administered intravenously or subcutaneously. CDEC also noted that while the heterogeneity between the berotralstat and C1-INH trials is significant, and thus an indirect treatment comparison (ITC) is unlikely to produce robust estimates of comparative efficacy or safety, fewer differences exist between berotralstat and lanadelumab trials, such that an ITC may have been possible.
- Although defining a specific threshold for the reduction in the number of HAE attacks is difficult, the clinical expert suggested that a minimum reduction of 50% in the number of HAE attacks for which acute treatment is required could be considered clinically meaningful. During the initial and reconsideration meetings, CDEC discussed the finding that, in the APeX-2 study, 33% more patients in the berotralstat 150 mg treatment group than the placebo group achieved at least a 50% reduction in HAE attacks relative to baseline, which might indicate that berotralstat is moderately effective in reducing HAE attacks. Although 58% of patients in the berotralstat 150 mg group reported at least a 50% reduction in attacks, it was noted that 25% of patients who received placebo also achieved a clinically relevant reduction in attacks.
- During the initial and reconsideration meetings, CDEC discussed that reducing the frequency of attacks was important, and that improvement of HRQoL is also important as the impact of HAE on HRQoL can be significant. However, neither study detected a statistically significant difference between groups in HRQoL, measured using the Angioedema Quality of Life Questionnaire (AE-QoL), or European Quality of Life – 5 Dimension (EQ-5D). CDEC noted the lack of consistently demonstrated benefit on HRQoL compared to placebo. In the APeX-2 study, both the placebo and berotralstat

group showed a mean change from baseline on the AE-QoL that exceeded the 6-point minimal important difference (MID), and it is unclear if the improvement observed can be attributed to the study drug or to other factors that are common to both the placebo and berotralstat groups.

- During reconsideration meetings, CDEC discussed the feedback received on the draft recommendation from the clinician groups regarding the need for both a non–plasma-derived and oral option for preventing HAE. CDEC discussed that this need was not reflected in the HRQoL data from the APeX-2 trial and that while objective evidence of an oral option improving HRQoL is absent, both the patient and clinical group feedback states that this is an important unmet need.
- During the initial and reconsideration meetings, CDEC discussed that no conclusions regarding the impact of berotralstat on hospitalization, emergency visits, or mortality could be made due to the lack of evidence.
- CDEC noted that the controlled data were limited to comparison with placebo for 24 weeks, where a total of 47 patients received berotralstat at the Health Canada–recommended dose. While longer-term, uncontrolled studies suggest that a [redacted] may be maintained in patients who continued on therapy for [redacted], due to the limitations associated with these data, there is uncertainty regarding the longer-term efficacy of berotralstat. During the reconsideration meetings, CDEC discussed that long-term extension data [redacted] did not demonstrate [redacted] in patients who persisted on treatment with berotralstat; however, this time point was associated with a [redacted].
- The number of patients included in the APeX-2 study who were younger than 18 years of age was small (2 per group); this was acknowledged by regulatory authorities and was considered to be reasonable given the rarity of HAE. The clinical expert indicated that most adolescents with HAE do not have a sufficient number of attacks to qualify to enter a trial, but noted that exposure in 4 patients may not be sufficient to identify rare side effects.

Background

HAE is a rare autosomal-dominant disorder that is characterized by recurrent attacks of nonpruritic subcutaneous or submucosal edema, most commonly affecting the skin (cutaneous attacks), gastrointestinal tract (abdominal attacks), and respiratory tract (laryngeal attacks). The reported prevalence of HAE ranges from 1 in 93,000 to 1 in 50,000. There are 3 types of HAE: type 1 (85% of patients) is caused by decreased secretion of complement 1 esterase inhibitor (C1-INH); type 2 (15% of patients) is characterized by normal or elevated production of functionally impaired C1-INH; and a third type, known as HAE with normal C1-INH (formerly referred to as type 3 HAE), is characterized by normal C1-INH level and function (prevalence is uncertain). Therapeutic options available in Canada for LTP treatment include C1-INHs, lanadelumab, oral attenuated androgens (e.g., danazol), and antifibrinolytics (e.g., tranexamic acid). The most commonly used treatments in Canada are C1-INHs, which act by replacing the missing or malfunctioning C1-INH protein, but all are derived from human plasma and are administered by IV or subcutaneous (SC) injection. Lanadelumab also requires SC administration. Oral danazol and tranexamic acid are not approved for use in HAE and are limited by frequent and potentially serious adverse effects or poor efficacy.

Berotralstat is a plasma kallikrein inhibitor that decreases plasma kallikrein activity and controls excess bradykinin generation in patients with HAE. The Health Canada indication is for the routine prevention of attacks of AE in adults and pediatric patients aged 12 years and older. Berotralstat is available as a 150 mg oral capsule and the recommended dose is 150 mg once daily. Health Canada states berotralstat should not be used for the treatment of acute HAE attacks, as the safety and efficacy for this use has not been established.

Sources of Information Used by the Committee

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

- a review of 2 double-blind, placebo-controlled, randomized controlled trials (RCTs) in patients aged 12 years and older with type 1 or 2 HAE
- patients' perspectives gathered by 1 patient group, HAE Canada
- input from public drug plans that participate in the CADTH review process
- input from 1 clinical specialist with expertise diagnosing and treating patients with HAE
- input from 1 clinician group, representing the Canadian Hereditary Angioedema Network
- a review of the pharmacoeconomic model and report submitted by the sponsor
- supplementary data from 1 open-label extension study
- information submitted as part of the request for reconsideration (described subsequently).

Stakeholder Perspectives

Patient Input

One patient group, HAE Canada (HAEC), submitted patient input for this review. HAEC is dedicated to creating awareness about HAE and other related angioedema, to help speed the diagnosis of patients, improve access to treatments, and enable patients to become champions for their own quality of life. The input was based on data collected from surveys in 2019 (n = 66) and 2021 (n = 138), qualitative interviews with 11 patients with a mix of either type 1 or type 2 HAE, and comments from 3 patients who had experience with the treatment under investigation in a clinical trial.

Respondents rated the impacts HAE had on their day-to-day activities on a scale from 1 (not at all) to 5 (significant impact), with weighted averages ranging from 2.20 for impacts on their ability to conduct household chores to 2.94 for impacting their ability to travel. The majority (62%) had to miss time from work due to HAE. Approximately 20% of patients reported that HAE required them to spend out-of-pocket for medical care; similarly, approximately 20% of patients were either very dissatisfied or dissatisfied with their current treatments. Among the 3 patients who had experience with berotralstat, 1 patient reported that the treatment was extremely effective in preventing attacks of HAE and that the adverse effects were easy to tolerate. Two patients did not find the treatment effective in the prevention of attacks of HAE.

According to the patient input received, a majority of patients are seeking treatments with an easier mode of delivery, and some prefer a product that is not plasma-derived. Patients continue to seek treatments that better control attacks while offering greater convenience and ease of use. Treatments that eliminate or substantially reduce attacks compared to existing treatments are of critical importance to patients, as each angioedema attack can be severely debilitating, and in many cases life-threatening. Greater control of attacks would also reduce the anxiety and fear many patients experience due to unpredictable attacks and reduce the negative impact on 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 by CADTH

According to the clinical expert consulted by CADTH, the treatment burden of the injectable products used for LTP therapy can be substantial, particularly for those who have difficulty with self-administration by IV or SC injection, and considering the frequency of administration of C1-INH. Although androgens are administered orally, they are associated with significant adverse effects, and are contraindicated in certain patient populations. The expert noted that berotralstat could be considered as a first-line option for LTP therapy, although it may not be the preferred option for use in patients who are pregnant or in patients younger than 12 years of age, due to limited clinical data.

The expert indicated that patients could be considered good candidates for treatment with berotralstat if they experience frequent HAE attacks that require acute treatment. The oral route of administration may be preferred for some patients and could be useful for patients who have to travel, where LTP with C1-INH may be impractical. The following patients may not be appropriate candidates for treatment with berotralstat: those who were misdiagnosed as having HAE, but actually have histaminergic chronic urticaria or histaminergic idiopathic angioedema; those with HAE but who only have mild and intermittent symptoms (i.e., on-demand therapy is sufficient); those who are currently well controlled and satisfied with their existing LTP therapy; and those who have a significant adverse reaction to berotralstat.

Prescribing of berotralstat should be limited to specialists with an expertise in the diagnosis and management of patients with angioedema, including immunologists, allergists, and hematologists. This will help ensure that the correct diagnosis has been made before initiating treatment with berotralstat and that the response to treatment is appropriately monitored. Response to treatment would be assessed based on a reduction in the frequency, severity, and duration of attacks. Patients and clinicians would also be seeking an increase in the ability to perform activities of daily living during attacks if these were previously affected. The expert noted that response to treatment with LTP such as berotralstat would be initially assessed after 3 months, with subsequent follow-up occurring every 6 or 12 months. The following were identified as situations in which discontinuing treatment with berotralstat could be appropriate: pregnancy, since adverse effects during pregnancy are unknown and C1-INH is the preferred option; intolerable adverse effects with berotralstat; or an inadequate response or loss of response (e.g., increase in attacks requiring rescue medication).

Clinician Group Input

Ten clinicians representing the Canadian Hereditary Angioedema Network (CHAEN) provided input for this review. They noted a need for a treatment to prevent attacks, improve the acute management of HAE, and provide convenient methods of self-administration. HAE patients

are at risk of experiencing a life-threatening laryngeal attack, which can have a considerable impact on their HRQoL. Furthermore, IV treatments may have the effect of requiring patients to spend extra time travelling to treatment appointments and undergoing treatment if they are unable to self-administer. Current off-label oral prophylaxis options for people living in Canada include androgen therapy, such as danazol. Androgens are associated with a range of severe adverse effects, including headaches, hypertension, weight gain, masculinizing effects for women, hepatocellular carcinoma, dyslipidemia, and cardiac disease. The input suggests that the treatment under review may provide a safe and effective oral prophylactic, which may be preferred to the current standard of care by some patients, particularly those who are averse to long-term injections. The input recommends that the treatment be considered for all patients who are candidates for LTP.

Drug Program Input

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

- relevant comparators
- 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
- care provision issues
- system and economic issues.

The clinical expert consulted by CADTH 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 APeX-2 trial was placebo controlled. Placebo may not be an appropriate comparator given the number of available therapies for prophylaxis of HAE. Approved LTP therapies for HAE include plasma-derived C1-esterase inhibitors. Lanadelumab (Takhzyro) is the only drug therapy approved for prophylaxis of HAE. Berinert IV (approved for treatment of acute attacks) has also been used off-label for LTP of HAE.	CDEC noted that placebo is not the most appropriate choice for comparison.
Plasma-derived C1-esterase inhibitors, such as Cinryze IV and Haegarda SC, are not funded by drug programs as they are plasma-derived products.	Comment from the drug programs to inform CDEC deliberations.
Considerations for initiation of therapy	
Berotralstat is not indicated by specific HAE type (i.e., type 1, 2, or HAE with normal C1-INH function). The ApeX-2 and ApeX-S trials enrolled patients with HAE type 1 and 2. Patients with HAE with normal C1-INH were not represented in either clinical	CDEC noted that the reimbursed population should align with the criteria used by each of the public drug plans for initiation, renewal, discontinuation, and prescribing of lanadelumab

Implementation issues	Response
trial; however, Health Canada indication does not specify HAE type for berotralstat. Would berotralstat be used in patients with HAE with normal C1-INH? Are results from the trials generalizable for patients with HAE with normal C1-INH? Lanadelumab is also indicated for prophylaxis of HAE (type not specified); However, the reimbursement recommendation for lanadelumab was specific for HAE type 1 and type 2. There is no consensus among clinical experts managing HAE on the specific number of attacks which corresponds to a threshold for initiation of LTP therapy. Is there a specific number of attacks which corresponds to a threshold for initiation of LTP therapy?	for the routine prevention of attacks of AE. The clinical expert noted to CDEC that berotralstat may theoretically be of benefit to HAE patients with normal C1-INH function, but there is currently no evidence to support its use in this population. There are other treatments available that may be more suitable options for patients with HAE and normal C1-INH. There is no specific number of attacks that is used as a threshold to initiate LTP, but often the criteria used in the clinical trials are used as a guide. Patients who experience less frequent but severe or disabling attacks may also benefit from long-term therapy.
Indicated for patients aged 12 years and older. In an international survey, patients with type 1 or type 2 HAE had a mean age of onset of 11.5 years, with a wide range from 0 to 58 years. Therefore, there is potential for requests for patients younger than what is specified by the indication. Would you treat patients who are younger than 12 years of age with berotralstat?	CDEC agreed with the clinical expert that data are lacking on the safety and efficacy of berotralstat in children younger than 12 years of age. Until safety data becomes available, berotralstat should not be used in this population.
No curative treatments are available for HAE. What is the treatment duration of LTP agents? Is treatment indefinite? Patients receiving berotralstat may have received a greater reduction in the number of attacks the longer therapy is maintained. An open-label trial for berotralstat up to 240 weeks has been completed. Is it expected that a greater reduction in number of attacks would be achieved if patients maintained longer-term therapy?	CDEC agreed with the clinical expert that LTP treatment is indefinite until a more effective treatment becomes available or patient's experience adverse effects with therapy. The clinical expert noted to CDEC that there are limitations in the longer-term berotralstat data. Dropouts for whom berotralstat was ineffective may have led to the greater reduction in attacks over time in the open-label studies. Further evidence is required on the longer-term effectiveness of berotralstat. The clinical expert also noted to CDEC that berotralstat is not replacing the missing or dysfunctional C1-INH, which is the underlying pathology of the disease. Thus, there is a risk that over time, patients on berotralstat may develop acquired angioedema or autoantibodies to C1-INH, which would lead to an increase in attacks. Additional trial data are required to determine if berotralstat may lose its effectiveness with longer-term use.
Should patients who do not respond to lanadelumab (no reduction from baseline number of attacks) be eligible for treatment with berotralstat? Is data available for switching between products for LTP of HAE? Can CDEC comment on patients switching? How should response to therapy be evaluated for patients who switch from injectable LTPs? Drug plans may not have baseline information for these patients before treatment is administered.	CDEC agreed with the clinical expert that patients not responding to lanadelumab may be switched to berotralstat, although clinical trial data demonstrating efficacy in this patient population are lacking. CDEC also noted that switching treatment is probably something that pragmatically would happen, so using a patient's historical HAE attack rate before

Implementation issues	Response
	initiating prophylactic therapy of any kind seems reasonable. The clinical expert also noted to CDEC that, for patients switching between LTP therapies, it is difficult to know the true (i.e., untreated) baseline rate of attacks. Thus, renewal criteria that include a specific response threshold that must be met may be difficult to implement in practice.
Alignment with lanadelumab may be considered if CDEC determines that both drugs are first-line therapies for LTP for HAE. The initiation criteria for lanadelumab are as follows: 1. The patient is at least 12 years of age. 2. The diagnosis of HAE type 1 or 2 is made by a specialist physician who has experience in the diagnosis of HAE. 3. 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 berotralstat be aligned with that of lanadelumab? If the recommendation for berotralstat is aligned for type of HAE (types 1 and 2), there will be a treatment gap for patients with HAE with normal C1-INH). Should a reimbursement recommendation for patients with HAE with normal C1-INH be considered? If considered for berotralstat, should it also be considered for lanadelumab? Both products have the Health Canada indication for prevention of HAE (not differentiated by type). Clinical trials have only included type 1 and type 2 patients. HAE type 1 makes up 85% of HAE patients. HAE type 2 makes up 15% of HAE patients. The prevalence of HAE with normal C1-INH (previously referred to as HAE type 3) is unknown, and there are unlikely to be clinical trials for this specific type.	The clinical expert indicated that patients who have experienced severe attacks (e.g., laryngeal attacks) should not be required to meet a minimum number of attacks to qualify for LTP. According to the clinical expert, berotralstat may theoretically be of benefit to HAE patients with normal C1-INH function, but there is currently no evidence to support use in this population. However, CDEC recommended that berotralstat be reimbursed in patients with similar characteristics to those enrolled in the ApeX-2 trial (i.e., patients with type 1 and 2 HAE), which is also aligned with the initiation criteria for lanadelumab.
Considerations for continuation or renewal of therapy	
Not all drug plans reimburse icatibant acetate (Firazyr), nor do all patients receive icatibant acetate for acute treatment. It may be difficult for drug plans to determine if patients are accessing acute injectable treatments, such as plasma-derived agents, through Canadian Blood Services (CBS). Drug plans may have to rely on physician reporting of this when assessing requests. Can CDEC include a discussion point regarding what reduction of HAE attacks would be indicative of as a response? Alignment with lanadelumab for response to therapy, with respect to reduction of HAE attacks being indicative of response, would be appropriate. Lanadelumab criteria vary across jurisdictions. Lanadelumab listing criteria in at least 2 jurisdictions stipulate a 50% reduction in HAE attacks within 3 months from baseline for renewal, and continued response is defined as maintenance of reduction of HAE attacks of at least 50% from baseline. Other jurisdictions do not specify a reduction in attacks for response.	According to the clinical expert, a 20% reduction in attack frequency is considered a mild improvement, 50% reduction is moderate, and 70% is considered marked improvement. The clinical expert noted that, for patients switching between LTP therapies, it is difficult to know the true (i.e., untreated) baseline rate of attacks. Thus, renewal criteria that include a specific response threshold that must be met may be difficult to implement in practice. CDEC recommended that the renewal criteria for berotralstat be aligned with the criteria for lanadelumab.

Implementation issues	Response
However, if a patient experiences and maintains a 30% reduction from baseline, should that be deemed a treatment failure, to warrant discontinuation of therapy? It may not be cost effective if a 50% reduction in HAE attacks is achieved.	
Renewal criteria for lanadelumab should be considered when considering renewal criteria for berotralstat. The renewal criteria for lanadelumab are as follows: 1. An assessment of a response to treatment should be conducted 3 months after initiating treatment with lanadelumab. 2. 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 of attacks observed before initiating treatment with lanadelumab. 3. Following the initial 3-month assessment, patients should be assessed for continued response to lanadelumab every 6 months. 4. 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 berotralstat be aligned with the criteria for lanadelumab? Should a specific reduction in HAE attacks, which is indicative of response, be considered for inclusion in the recommendation? A specific reduction in HAE attacks, which is indicative of response, may be considered for inclusion in the recommendation. In general, it is helpful for assessment if the baseline time frame aligns with the renewal assessment time frame (i.e., baseline is the number of attacks in 3 months). Renewal assessment at 3 months evaluates the number of attacks while on treatment within 3 months.	CDEC agreed with the clinical expert that it would be reasonable to align the renewal criteria for berotralstat with those used for lanadelumab. The clinical expert noted the difficulty in defining specific response criteria in cases where the untreated baseline attack rate was unclear.
Considerations for discontinuation of therapy	
Consistency with discontinuation criteria for lanadelumab may be considered. However, it may be helpful for jurisdictions to have additional clarification around inadequate response or loss of response as a discussion point. 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: 1. 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. 2. 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 berotralstat be aligned with the discontinuation criteria for lanadelumab? Are the definitions of inadequate response or loss of response in the preceding bullet points appropriate?	CDEC agreed with the clinical expert that it would be reasonable to align the discontinuation criteria for berotralstat with those used for lanadelumab.

Implementation issues	Response
Considerations for prescribing of therapy	
There are limited numbers of allergists and immunologists in some regions, and if restricted, access may be an issue. With previous comparators, there have been specialized general practitioners or internists with experience in prescribing who have been identified to have expertise in management of HAE. The lanadelumab recommendation specifies specialist physicians who have experience in the diagnosis of HAE. Would this be appropriate for berotralstat as well?	CDEC agreed with the clinical expert that prescribing should be limited to specialists with an expertise in the diagnosis and management of patients with angioedema, including immunologists, allergists, and hematologists.
Berotralstat is the first oral plasma kallikrein inhibitor. There may be risk of combination therapy with lanadelumab, as it has a different mechanism of action. In practice, will berotralstat be used in combination with other prophylactic treatments for HAE, such as lanadelumab? In addition, there is a risk that berotralstat may be used in combination with plasma-derived proteins. This would be difficult for drug plans to determine if patients are using plasma-based products, as they are funded through a different mechanism. Berotralstat may also be used in combination with icatibant acetate if attacks do occur despite prophylaxis. Can short-term prophylaxis be used in combination with LTP therapy? The aim of short-term prophylaxis is to minimize the risk of attacks when exposure to a potential or known trigger is anticipated.	The clinical expert noted to CDEC that combination LTP therapy is possible, although data supporting add-on therapy is limited. Short-term prophylaxis may be used in combination with LTP therapy. All patients require access to treatments to manage acute attacks. However, CDEC noted that there is no evidence available to support the use of berotralstat in combination with other agents used for LTP, and hence CDEC recommended that berotralstat should not be used in combination with other medications used for long-term prophylactic treatment of angioedema (e.g., C1-esterase inhibitors or lanadelumab).
What is the place in therapy for berotralstat vs. lanadelumab?	CDEC agreed with the clinical expert that berotralstat and lanadelumab have a similar place in therapy.
Generalizability	
How should patients who are wanting to switch from lanadelumab to berotralstat be assessed, as a baseline number of attacks is assessed before starting therapy? If they are attack-free for a period of time, should switching be considered? Patients may desire to be switched to an oral therapy.	CDEC agreed with the clinical expert that, when switching patients between LTP therapies, response should be based on the attack rate before starting any prophylaxis. Some patients may prefer an oral treatment vs. an injectable treatment, even if berotralstat is not as effective as other options.
If the recommendation excludes HAE patients with normal C1-INH, this would deviate from the Health Canada indication and may create a need to consider requests outside of criteria.	Comment from the drug programs to inform CDEC deliberations.
Care provision issues	
Injection site reactions from alternative products may be a rationale for patients to switch to berotralstat. In clinical trials, adverse events from berotralstat did not result in discontinuations.	Comment from the drug programs to inform CDEC deliberations.
System and economic issues	
The budget impact is difficult to interpret or validate, as it includes products provided through both CBS and drug plans.	Comment from the drug programs to inform CDEC deliberations.

Implementation issues	Response
The plasma-derived products (C1-INHs) are reimbursed through CBS and Héma-Québec. The non–plasma-based products, icatibant acetate (for treatment of acute attacks) and lanadelumab (for prophylaxis) are reimbursed through drug plans. When lanadelumab was implemented, it was anticipated that use of the plasma-derived products might be reduced with increasing uptake of lanadelumab. This was an increased cost to drug plans, but potentially cost offsets elsewhere were realized through the reduction of blood products funded through CBS. Berotralstat, if listed, may have a similar effect of shifting cost from blood products to drug programs. It may be to a lesser extent as it is a second entry product.	Comment from the drug programs to inform CDEC deliberations.
Lanadelumab has successfully completed pCPA negotiations. Icatibant acetate has also successfully completed pCPA negotiations. Plasma-derived products are procured through purchase agreements through CBS.	Comment from the drug programs to inform CDEC deliberations.
It may be easier for some patients to access products through CBS vs. products reimbursed through drug plans with strict reimbursement criteria (e.g., lanadelumab).	Comment from the drug programs to inform CDEC deliberations.
Having berotralstat available may reduce the potential risk of drug shortages of plasma-derived products. An oral product may reduce health system costs of administration and increase accessibility for patients. Patients accessing products through CBS may have no copay associated with therapy. Listed drug products may be subject to a patient's copay or deductible; therefore, the cost to the patient may increase when switching from a product available through CBS to a product available through a drug plan.	Comment from the drug programs to inform CDEC deliberations.

C1-INH = complement 1 esterase inhibitor; CBS = Canadian Blood Services; CDEC = CADTH Canadian Drug Expert Committee; HAE = hereditary angioedema; LTP = long-term prophylactic; pCPA = Pan-Canadian Pharmaceutical Alliance; SC = subcutaneous.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

The systematic review included 2 double-blind RCTs that evaluated the efficacy and safety of berotralstat versus placebo in patients aged 12 years and older with type 1 or 2 HAE who experienced at least 2 investigator-confirmed HAE attacks during the run-in period. The APeX-2 and APeX-J studies randomized patients to placebo, berotralstat 110 mg, or berotralstat 150 mg daily for 24 weeks (part 1), after which all placebo patients were randomized to berotralstat 110 mg or 150 mg daily, and those on active drug continued with the same dose for part 2 (double-blind, up to week 48 [APeX-2] or week 52 [APeX-J]). In the subsequent part 3 of the trials, all patients were switched to open-label berotralstat 150 mg daily (up to week 240 [APeX-2] or week 104 [APeX-J]). During the trials, all patients had access

to standard of care treatments for acute HAE attacks (e.g., C1-INH or icatibant acetate). The primary outcome in both studies was the rate of investigator-confirmed HAE attacks over 24 weeks (part 1). All patient-reported HAE attacks were confirmed by the investigator and had to include symptoms of swelling, which could be visible swelling or symptoms in the oropharyngeal or abdominal regions that were indicative of internal swelling. This review focused on the comparison between berotralstat 150 mg and placebo at 24 weeks, which included 80 patients from the APeX-2 study and 13 patients from the APeX-J study. Data from the berotralstat 110 mg group has not been summarized in this report, since this dose has not been approved by Health Canada.

The APeX-2 study was conducted in 11 countries, including Canada (3 sites), the US, and several countries in Europe (Germany, Romania, the UK, France, Spain, Hungary, Macedonia, Czech Republic, and Austria). The mean age of patients enrolled was 40.0 years (standard deviation [SD] = 14.0) in the berotralstat 150 mg group and 44.5 years (SD = 14.1) in the placebo group. Patients were predominantly female (58% and 68%) and white (95% and 93%), with a mean baseline rate of 3.1 (SD = 1.6) and 2.9 (SD = 1.1) investigator-confirmed HAE attacks per month in the berotralstat 150 mg and placebo groups, respectively.

The APeX-J study was conducted at multiple centres in Japan. The enrolled patients had a mean age of 37.3 years (SD = 9.1) in the berotralstat 150 mg group and 42.3 years (SD = 13.5) in the placebo group. Most patients were female (86% and 83%) and Asian (86% and 100%) in the berotralstat and placebo groups, respectively. At baseline, the mean number of expert-confirmed attacks per month was 2.0 (SD = 1.1) in the berotralstat 150 mg group and 2.5 (SD = 1.5) in the placebo group.

Efficacy Results

In the APeX-2 study, the rate of investigator-confirmed HAE attacks per month was 1.31 for the berotralstat 150 mg group and 2.35 for the placebo group, during the 24-week double-blind treatment period. The relative rate reduction was 44.2% (95% CI, 23.0% to 59.5%; P < 0.001) for berotralstat 150 mg versus placebo. The results of the primary outcome were similar in the APeX-J study, which reported 1.11 and 2.18 expert-confirmed HAE attacks per month in the berotralstat 150 mg and placebo groups, respectively, and a rate reduction of 49.1% (95% CI, 20.4% to 67.5%; P = 0.003).

In the APeX-2 study, 58% of patients in the berotralstat 150 mg group and 25% in the placebo group achieved at least a 50% relative reduction in the rate of investigator-confirmed HAE attacks compared to baseline (odds ratio [OR] = 3.91; 95% CI, 1.51 to 10.16; P = 0.005). However, these analyses were not adjusted for multiple testing and should be interpreted with caution because of the potential for inflated type I error rate.

[redacted] in the berotralstat 150 mg group [redacted] of the APeX-2 study, and 1 patient in the placebo group (2.6%) had no investigator-confirmed HAE attacks during the 24-week treatment period. [redacted] in the APeX-J study reported [redacted] during the first 24 weeks of treatment.

The number and proportion of days with HAE symptoms during the first 24 weeks was a secondary outcome in the APeX-2 study. Patients in the berotralstat 150 mg group reported a mean of 19.4 days (SD = 21.5) with HAE symptoms compared to 29.2 days (SD = 24.3) for patients in the placebo group. The least squares (LS) mean difference in the proportion of days with symptoms was −0.078 (95% CI, −0.133 to −0.023), which translates to approximately 13 fewer symptom-days (out of a total of 169 treatment days)

in the berotralstat group versus the placebo group. Although the proportion of days with HAE symptoms favoured berotralstat over placebo, the data should be interpreted as indeterminate due to failure of a prior outcome in the statistical analysis hierarchy. In the APeX-J study, no statistically significant difference was detected between groups in the proportion of days with HAE symptoms (LS mean difference = −0.122; 95% CI, −0.280 to 0.036; P = 0.12).

HRQoL was measured using the Angioedema Quality of Life Questionnaire (AE-QoL). While both the berotralstat 150 mg and placebo groups in the APeX-2 study reported improvements in AE-QoL total scores at week 24 relative to baseline, no statistically significant difference was detected between groups in the LS mean difference (−4.9 points; 95% CI, −12.2 to 2.4; P = 0.19). In the APeX-J study, the LS mean difference for the change from baseline in the AE-QoL total score was −19.0 (95% CI, −39.0 to 1.0).

New information supplied by the sponsor as part of the request for reconsideration showed that, during part 2 of the APeX-2 study (week 24 to 48), the mean investigator-confirmed attack rate per month in the berotralstat 150 mg group was 1.7 (SD [redacted]) at 24 weeks (n = 37), and 1.1 (SD [redacted]) at week 48 (n = 31). The mean number of days with angioedema symptoms during part 2 was [redacted] days (SD [redacted]), and the proportion of days with symptoms was [redacted] (SD [redacted]) for patients in the berotralstat 150 mg group. Among the patients switched from placebo to berotralstat 150 mg at week 24 (n = 17), the mean attack rate per month was 2.6 events (SD [redacted]) at 24 weeks (i.e., start of active treatment), and 0.6 events (SD [redacted]; n = 14) at 48 weeks. The proportion of days with angioedema symptoms was [redacted] (SD [redacted]) for patients switched to berotralstat 150 mg. Overall [redacted] of patients completed part 2 of the study, with [redacted] patients ([redacted]) stopping therapy due to adverse events or lack of efficacy, and [redacted] others ([redacted] stopping for other reasons.

Among the [redacted] patients who entered part 3 of the APEX-2 study and received open-label berotralstat 150 mg daily, the overall adjusted patient-reported HAE attack rate was [redacted] events per month (SD [redacted]) while patients remained on treatment. The mean number of days with angioedema symptoms was [redacted] days (SD [redacted]), which corresponds to a proportion of days of [redacted](SD [redacted]). During part 3, [redacted] patients ([redacted]) stopped treatment for the following reasons: [redacted]

Harms Results

Adverse events were reported by 85% of patients in the berotralstat 150 mg group and 77% of those in the placebo group during the first 24 weeks of the APeX-2 study. The most frequently reported events in the berotralstat group were nasopharyngitis (23%), nausea (15%), vomiting (15%), and diarrhea (13%). Gastrointestinal adverse events were reported more frequently among patients who received berotralstat 150 mg compared to placebo (50% versus 36%).

No patients in the berotralstat group experienced a serious adverse event during the first 24 weeks of the APeX-2 study, whereas 3 patients in the placebo group experienced 4 serious adverse events of uterine leiomyoma, diverticulum intestinal hemorrhage, pneumonia, and transient ischemic attack. One patient in the berotralstat 150 mg group stopped treatment due to abnormal liver function tests, and 1 patient in the placebo group stopped the study drug due to a depressive episode. No deaths were reported, and no new safety signals were

identified in part 2 [redacted] of the APeX-2 trial among patients who received berotralstat 150 mg [redacted]

All patients in the APeX-J study experienced 1 or more adverse events in the first 24 weeks. Gastrointestinal adverse events were reported by 43% of patients in the berotralstat 150 mg group, compared to 17% of patients in the placebo group. One placebo-treated patient stopped treatment due to urticaria, and no patients stopped treatment in the berotralstat 150 mg group. No serious adverse events were reported.

Critical Appraisal

Both RCTs were conducted using a similar 3-part study design and comparable statistical methods. Patients were allocated to treatment groups using appropriate methodology, with randomization stratified by a relevant prognostic factor (i.e., baseline HAE attack rate). Due to the small sample size of the trials (40 or 7 patients per treatment group), randomization may not ensure the groups were balanced for all measured or unmeasured prognostic factors or confounders, and at baseline, imbalances between treatment groups were observed for some patient characteristics. In addition, more patients in the placebo group of the APeX-2 study stopped treatment or withdrew before 24 weeks, which also may contribute to imbalances between groups. However, the impact of these differences on the study's findings is unclear, and sensitivity analyses that explored different missing data assumptions were generally supportive of the primary analyses [redacted]

The primary outcome (investigator-confirmed HAE attack rate over 24 weeks) was considered to be clinically relevant by the expert consulted by CADTH. Other outcomes of interest to this review (e.g., laryngeal attacks, treated or severe attack rate, and the responder analyses) were either exploratory or ad hoc outcomes, and these analyses were not included in the hierarchical statistical analysis. Therefore, any analyses with P values lower than 0.05 should be interpreted with caution because of the potential for inflated type I error rate. Although the AE-QoL questionnaire has been used in clinical trials of other HAE treatments, the instrument contains domains that are not specific to HAE. Neither study were designed to test for differences in the need for hospitalization or emergency visits, or mortality. As with most clinical trials, the studies were not powered to detect infrequent adverse effects or those with a lag time.

Although the data from part 2 [redacted] of the APeX-2 study suggest that patients who continued on berotralstat 150 mg may maintain a reduction in HAE attacks, the data were limited by potential selection and reporting bias and the lack of a comparator group. Investigators and patients were aware that patients were receiving active treatment, and thus their expectations of treatment could affect reporting of subjective outcomes, such as symptoms of swelling or adverse effects. Moreover, HAE attacks in part 3 were not adjudicated by the investigator but were based on patient-reported events; thus, attack events analyzed in part 3 may not be comparable to the investigator-confirmed events in part 1 and part 2. In [redacted] part 2 [redacted], the efficacy analyses were reported descriptively based on observed data with no imputation for missing data, and with no sensitivity analyses to assess the robustness of the results. Given the attrition observed, the results reported may overestimate the treatment effects and underreport adverse effects, as patients who are

tolerant of therapy and showed adequate response were more likely to continue in the trial. Finally, part 2 [redacted] were uncontrolled which makes the change in HAE attack rate difficult to interpret, particularly since HAE attacks are sporadic and may fluctuate throughout the year, owing to exposure to seasonal triggers, hormonal changes, or other factors.

With regard to external validity, the findings of the pivotal APeX-2 study were reflective of the enrolled participants, who were patients with type 1 or 2 HAE who had, on average, 3 HAE attacks per month, most of whom had experienced a prior laryngeal attack. The trial included patients who were medically appropriate for on-demand treatment as the sole management of HAE, and thus may have excluded patients with more severe HAE who could not tolerate discontinuation of current LTP therapy. Compared to the overall population in Canada, the racial diversity in the APeX-2 trial was limited, as most patients were white (94%). In addition, patients were predominantly female (63%) and aged between 18 and 65 years. Only 4 adolescents and 4 patients older than 65 years of age were enrolled in the berotralstat 150 mg and placebo groups; therefore, there is limited data to extrapolate to the younger and older age groups. The APeX-J study provided additional data from 13 patients in Japan. These patients were generally similar to those in the pivotal study, although the patients' weight and body mass index (BMI) were lower, as was the mean baseline HAE attack rate. Overall, the clinical expert felt that the characteristics of the patient population enrolled in the trials offered a good representation of the target population, and did not identify any issues that could substantially limit the generalizability of the findings.

There is no direct evidence comparing berotralstat to other LTP therapies. The comparative evidence was limited to two 24-week randomized, placebo-controlled trials, in which a total of 47 patients received berotralstat 150 mg daily.

Indirect Comparisons

The sponsor conducted a feasibility assessment to determine if the clinical trials for treatments used for routine prevention of HAE attacks were sufficiently similar to permit valid comparison in an ITC. The authors of the feasibility assessment identified a number of important differences in the study design and patient characteristics of the trials, and concluded that it was not possible to generate robust estimates of the comparative treatment effects due to between-study heterogeneity. Based on the information presented in the sponsor's feasibility assessment, the CADTH reviewer agrees that the heterogeneity between the berotralstat and C1-INH trials is significant, and thus any ITC is unlikely to produce robust estimates of comparative efficacy or safety. However, fewer differences exist between berotralstat and lanadelumab trials, such that an ITC may have been possible.

Other Relevant Evidence

Data from 1 open-label, long-term study were summarized in this report.

Description of Studies

The APeX-S study is an ongoing, uncontrolled, phase II study, which was conducted to evaluate the safety and efficacy of berotralstat in adults and pediatric patients aged 12 years or older with type 1 or 2 hereditary angioedema. In this study, 127 patients were enrolled from either a prior berotralstat trial or were recruited from the community, and all received open-label berotralstat 150 mg once daily for up to 48 weeks (interim analysis). At baseline, the median age was 44.0 years (range, 12 years to 72 years) and the majority of patients were female (61%), white (87%), and had a family history of HAE (80%).

Efficacy Results

From the beginning of the study through to week 48, there were a total of [redacted] adjusted HAE attacks reported among patients who received berotralstat 150 mg daily. The mean attack rate was 1.36 (SD = 1.51) attacks per month and the median attack rate was 0.93 (range, 0 to 7.6) attacks per month.

Harms Results

During the 48-week period, 91% of patients in the berotralstat 150 mg group reported 1 or more adverse events, the most common being nasopharyngitis (34%), headache (15%), and diarrhea (14%). Overall, 44.9% of patients experienced gastrointestinal adverse events. A total of 9% of patients experienced a serious adverse event, with [redacted] experiencing an HAE attack requiring hospitalization. No deaths were reported.

Critical Appraisal

This study was limited by the open-label design and lack of randomization or control group. Moreover, there is potential selection and attrition bias. A total of 24% of patients treated with berotralstat 150 mg discontinued the long-term study, mainly due to adverse events or a lack of perceived efficacy. This attrition could have resulted in a population of patients who were more tolerant of and responsive to berotralstat, which could lead to biased estimates of efficacy and safety.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adults and pediatric patients aged 12 years and older
Treatment	Berotralstat plus acute treatment of HAE attacks as they occur
Submitted price	Berotralstat, 150 mg, oral capsule: $850.00 per capsule
Treatment cost	The cost of berotralstat is $310,463 per year.
Comparators	• No LTP treatment management, including the avoidance of known triggers plus acute treatment of HAE attacks as they occur • Lanadelumab and C1-INHs (Cinryze, Berinert, and Haegarda) in combination with acute treatment of HAE attacks were considered in a scenario analysis
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (58 years)
Key data source	Clinical efficacy for patients receiving berotralstat and no LTP was modelled based on patient-reported HAE attack rates from the APeX-2 clinical trial.

Component	Description
Key limitations	• Based on the CADTH clinical review, the comparative clinical efficacy of berotralstat in comparison to other LTP treatments (lanadelumab, Cinryze, Berinert, and Haegarda) is unknown. The CADTH critical appraisal noted that a focused ITC may have been possible between berotralstat and lanadelumab, although this was not considered by the sponsor. Other LTP treatments, such as danazol and tranexamic acid, were also excluded from the scenario analysis in which other LTP treatments were considered as comparators, and as such the scenario does not reflect current clinical management. Any conclusions about the incremental cost-effectiveness of berotralstat in comparison to any LTP treatments available in Canada are therefore unknown. • The CADTH clinical review concluded that berotralstat results in modest reductions in HAE attacks in comparison to placebo. However, no LTP is an infrequently used comparator relative to active treatments and has limited clinical relevance for patients seeking treatment. Given the availability of various approved LTP treatments, patients would likely switch treatments upon treatment failure or discontinuation due to other reasons. The sponsor's assessment of berotralstat in comparison to no LTP may affect the interpretability of the sponsor's cost-effectiveness analysis in the context of clinical practice. • Attack rates used in the model were patient-reported and assumed to remain constant beyond the duration of the pivotal trial of 24 weeks. Investigator-confirmed attack rates are preferable to reduce potential bias and minimize the likelihood of patient errors in reported attacks related to misidentification of symptoms. The CADTH clinical review also concluded that patient dropout due to lack of response or intolerance may have overestimated the efficacy of berotralstat. There is no available evidence to suggest this sustained treatment benefit is clinically feasible given berotralstat's mechanism of action and lack of long-term efficacy data. Consequently, the estimated cost-effectiveness is likely biased in favour of berotralstat. • The submitted model based on being attack-free or experiencing an attack omits critical aspects of disease management relevant to patients, such as chronic abdominal symptoms and tracheotomy. The proportions of patients receiving various rescue medications for acute HAE attacks also did not reflect expected use in clinical practice, given that clinical expert feedback indicated that they would not differ based on the LTP treatment received. • Health utility values derived by the sponsor were limited by uncertainty and it is unclear if the values reflect the preferences of patients with HAE in Canada. • The sponsor's use of relative dose intensity (RDI) may underestimate drug costs for berotralstat and does not account for other factors that influence dosing, such as dose delays, reductions, or escalations. The sponsor also failed to account for drug wastage for IV treatments, although vial sharing for comparator products was not anticipated.
CADTH reanalysis results	• To account for key limitations, the CADTH base case incorporated investigator-confirmed attack rates for berotralstat and no LTP for up to 6 months of available data from the pivotal trial; adjusted subsequent rescue therapy use to reflect clinical practice (50% Berinert and 50% icatibant for all patients); and increased RDI to 100% while incorporating drug wastage for IV products. • In the CADTH base case, the ICER for berotralstat compared to no LTP was $14,559,490 per QALY gained (incremental costs: $8,851,166; incremental QALYs: 0.61). To achieve a mean ICER of $50,000 per QALY, a price reduction of approximately 93% is required for berotralstat. • A scenario analysis that assessed the inclusion of single-arm, investigator-confirmed attack rates for berotralstat extending from 6 months to 12 months resulted in an ICER of $7,848,146 per QALY for berotralstat compared to no LTP. • Additional scenario analyses were conducted, but the assessment of the cost-effectiveness of berotralstat is highly limited by the lack of comparative clinical evidence. Therefore, there is no evidence to support a price premium of berotralstat in comparison to other LTP treatments.

C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema; ICER = incremental cost-effectiveness ratio; LY = life-year; LTP = long-term prophylaxis; QALY = quality-adjusted life-year; RDI = relative dose intensity.

Budget Impact

CADTH identified key limitations with the sponsor's analysis related to the likely underestimation of market uptake for berotralstat; the underestimation of prevalence of HAE in Canada; uncertainty in the proportion of patients eligible for public coverage to determine the target population; and lack of clarity surrounding discontinuation criteria for berotralstat, which may be a driver of budget impact estimates. A CADTH reanalysis increased the market shares for berotralstat and prevalence of HAE in Canada. Although the sponsor suggested that berotralstat would be associated with a budget impact of $14,164,290 over the 3-year time horizon, based on the CADTH combined exploratory reanalysis, the reimbursement of berotralstat for the treatment of HAE in adults and pediatric patients aged 12 years and older would be associated with a budgetary increase of $24,529,115 in year 1, $31,074,770 in year 2, and $37,288,339 in year 3, for a 3-year total of 92,892,224. CADTH found the budget impact of berotralstat to be sensitive to market shares, prevalence of HAE, and proportion of patients eligible for public coverage.

Request for Reconsideration

The sponsor filed a request for reconsideration for the draft recommendation for berotralstat for the routine prevention of attacks of HAE in adults and pediatric patients aged 12 years and older. In their request, the sponsor identified the following issues:

- rationale and appropriateness of placebo control in the APeX-2 study
- feasibility of generating direct or indirect comparative evidence
- CADTH's assessment of the representativeness of the APeX-2 trial population to patients with HAE in Canada
- CDEC's assessment of the clinical meaningfulness of the reduction in HAE attack frequency observed in the APeX-2 study
- CDEC's assessment of the impact of berotralstat on HRQoL as observed in the APeX-2 study
- sponsor-provided, updated data on the longer-term safety and efficacy of berotralstat from the extension phase of the APeX-2 study
- CDEC's assessment of how berotralstat may meet the unmet needs in patients with HAE.

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

- feedback from the sponsor
- information from the initial submission relating to the issues identified by the sponsor
- feedback from 1 clinical specialist with expertise in the management of patients with HAE
- feedback from the public drug plans
- feedback from 1 clinician group: CHAEN
- feedback from 2 patient groups: Hereditary Angioedema Canada and Angio-Oedème Héréditaire du Québec.

All stakeholder feedback received in response to the draft recommendation from patient and clinician groups and the public drug programs is available on the CADTH website.

CDEC Information

Initial Meeting Date: July 28, 2022

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed

Regrets: 2 expert committee members did not attend.

Conflicts of interest: None

Reconsideration Meeting Date: December 21, 2022

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed

Regrets: 1 expert committee member did not attend.

Conflicts of interest: None