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CADTH Reimbursement Recommendation

Atogepant (Qulipta)

Indication: For the prevention of migraine in adults who have at least 4 migraine days per month
Sponsor: AbbVie Inc.
Final recommendation: Reimburse with conditions

Summary

What Is the CADTH Reimbursement Recommendation for Qulipta?

CADTH recommends that atogepant (Qulipta) be reimbursed by public drug plans for the prevention of migraine if certain conditions are met.

Which Patients Are Eligible for Coverage?

For migraine prevention, Qulipta should only be covered in adult patients who have tried at least 2 other types of treatments for the prevention of migraine.

What Are the Conditions for Reimbursement?

Qulipta should only be reimbursed if it is prescribed by a prescriber with experience managing chronic migraine (CM) headaches and if the cost of Qulipta is not more than the least costly calcitonin gene–related peptide (CGRP) inhibitor currently funded for this population. Qulipta should not be reimbursed for use in combination with other CGRP inhibitors for the prevention of migraine in adult patients with CM.

Why Did CADTH Make This Recommendation?

- Evidence from 1 clinical trial demonstrated that Qulipta reduced the symptoms of migraine, the number of migraine days, and acute medication use days per month, and also improved function. The evidence indicated that Qulipta was well tolerated, and the oral formulation may provide convenience of administration to patients.
- Based on CADTH's assessment of the health economic evidence, Qulipta may 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 Qulipta compared with other CGRP inhibitors, so the cost of Qulipta should not be greater than the least expensive CGRP inhibitor currently funded.
- Based on public list prices, Qulipta is estimated to lead to approximately $1 million dollars in cost savings for the public drug plans over the next 3 years.

Additional Information

What Is Chronic Migraine?

Migraine is a type of headache characterized by recurrent attacks of pulsating pain on 1 side of the head. Episodes can last from 4 to 72 hours, if untreated. The severity of pain ranges from moderate to severe, and it may be accompanied by increased sensitivity to light, sound, and

Summary

odours, as well as nausea, vomiting, numbness, and auras. In Canada, it is estimated that migraine affects 1 person in 10, and women are more likely than men to be affected.

Unmet Needs in Chronic Migraine

Many patients have difficulties finding effective treatments and need to try several medications before realizing benefit. Furthermore, conventional treatments for migraine prevention are available for oral administration but are associated with unwanted side effects.

How Much Does Qulipta Cost?

Treatment with Qulipta is expected to cost $6,735 per patient per year.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that atogepant be reimbursed for the prevention of migraine in adults with CM only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One randomized placebo-controlled trial (the PROGRESS trial) demonstrated that the use of atogepant 60 mg once daily in patients in whom 2 or more migraine prevention medications with different mechanisms of action had previously failed (N = [redacted]) resulted in added clinical benefit when compared with placebo. The evidence from the trial showed that, after 12 weeks of treatment, atogepant reduced monthly migraine days (MMDs) and monthly headache days (MHDs). In the full set analysis of the primary end point of the PROGRESS trial, the reduction in MMDs from baseline was higher for patients treated with atogepant 60 mg once daily than those who received placebo, with least squares mean difference (LSMD) of −1.82 days (95% confidence interval [CI], −2.89 to −0.75 days). In the population of patients in whom 2 or more medications had failed in the PROGRESS study, the reduction in MMDs from baseline was higher for patients treated with atogepant 60 mg once daily than those who received placebo, with LSMD in change from baseline in mean MMDs of [redacted] days (95% CI, [redacted] to [redacted] days). In the same group, the proportion of patients experiencing at least a 50% reduction in MMDs was greater with atogepant 60 mg once daily than with placebo ([redacted] versus [redacted], respectively). The odds of achieving at least a 50% reduction in MMDs was higher with atogepant 60 mg once daily than with placebo (odds ratio [OR] = [redacted]; 95% CI, [redacted] to [redacted]).

Patients and clinical experts identified the need for different treatment options. CDEC concluded that atogepant 60 mg once daily met some of the needs identified by patients, including reduction in the mean number of migraine days, headaches, and days of medication use per month, as well as improvement in function, with the convenience and ease of administration of an oral medication.

At the sponsor-submitted price for atogepant and publicly listed price for all comparators, atogepant was less costly than fremanezumab, eptinezumab, and galcanezumab, and more costly than onabotulinumtoxinA. Given that there is insufficient evidence to support a clinical benefit with atogepant compared with relevant comparators, the total drug cost of atogepant should not exceed the total drug cost of the lowest-cost CGRP inhibitor reimbursed for the prevention of CM in the population considered in this reimbursement request.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation, renewal, and prescribing		
1. Eligibility for reimbursement of atogepant should be based on the criteria used by each of the public drug plans for initiation, renewal, and prescribing of other CGRP inhibitors currently reimbursed for the prevention of migraine in adult patients with chronic migraine, with the addition of condition 2 for prescribing.	There is no evidence that atogepant should be held to a different standard than other CGRP inhibitors currently reimbursed when considering initiation, renewal, and prescribing. The clinical expert noted that the place in therapy for atogepant is comparable to other CGRP inhibitors.	—
2. Atogepant should not be reimbursed for use in combination with other CGRP inhibitors for the prevention of migraine in adult patients with chronic migraine.	No evidence was identified to demonstrate whether atogepant offers additional benefit when used in combination with other CGRP inhibitor treatments.	—
Pricing		
3. The price of atogepant should be negotiated so that it does not exceed the drug program cost of treatment with the least costly CGRP inhibitor reimbursed for the treatment of chronic migraine.	There is insufficient clinical evidence to justify a cost premium for atogepant over the least expensive CGRP inhibitor reimbursed for chronic migraine.	—

CGRP = calcitonin gene–related peptide.

Discussion Points

- CDEC noted that the PROGRESS trial did not calculate the sample size needed to detect statistically significant differences in the estimate of effects in the population of patients in whom 2 or more migraine prevention medications with different mechanisms of action had previously failed that is the focus of the reimbursement request. However, the committee discussed that atogepant had consistent and larger effects in this subgroup compared with the full set analysis across all main end points, and that the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) assessment showed moderate certainty for both the main population and the subgroup, indicating that atogepant likely has a beneficial clinical effect in the population of patients with migraine in whom 2 or more migraine prevention medications had previously failed.
- CDEC noted that the PROGRESS trial did not compare atogepant 60 mg once daily with other available active interventions. The committee observed that the effect estimates from the sponsor-submitted indirect treatment comparisons (ITCs) of atogepant with other interventions available in Canada (galcanezumab, fremanezumab, erenumab, onabotulinumtoxinA, or eptinezumab) had uncertainties due to highly imprecise estimates (wide credible intervals [CrIs]) that limit the ability to draw conclusions. Therefore, the committee concluded that there was insufficient evidence to

determine the effectiveness of atogepant compared with other interventions for migraine currently reimbursed in Canada.

- The committee observed that the results of the PROGRESS study suggested that treatment with atogepant 60 mg once daily may improve disability and function scores and measures of health-related quality of life, while reducing MHDs, monthly acute medication use days, and the impact of migraine on daily functioning. CDEC concluded that, although atogepant does not impact the underlying cause of migraine, it is a new oral option that addresses some unmet needs and may improve control and reduce the burden of migraines for patients and their caregivers.
- CDEC discussed the uncertainty in the economic analysis, notably that a cost-minimization approach is predicated on the assumption of clinical similarity between atogepant and relevant comparators. If atogepant confers differential efficacy or safety compared with the other CGRP inhibitors, the cost-effectiveness of atogepant, relative to other CGRP inhibitors used in the population considered in this reimbursement request, is unknown.

Background

Migraine is a multifactorial, disabling neurologic disease affecting 8% of the population of Canada, characterized by recurrent and often debilitating headaches of moderate to severe intensity accompanied by neurologic symptoms. Migraine is commonly categorized, according to the frequency of attacks, as episodic migraine (EM) or CM. People with migraine who have fewer than 15 MHDs are commonly referred to as having EM. CM has been defined as headaches occurring on 15 or more days per month for more than 3 months, of which at least 8 days per month have the features of migraine attacks. As attack frequency or severity increases, migraine management requires the use of both acute and preventive treatments. Multiple pharmacologic options for migraine prevention are currently available in Canada for patients with CM, including established oral preventive treatments, injectable onabotulinumtoxinA, or self-injectable and infusion CGRP monoclonal antibodies.

Atogepant is a CGRP receptor antagonist that has been approved by Health Canada (Notice of Compliance on May 2, 2024) for the prevention of migraine in adults who have at least 4 MMDs. Atogepant is available as oral tablets in 10 mg, 30 mg, and 60 mg doses, and the dosage recommended in the product monograph is 60 mg once daily.

Sources of Information Used by the Committee

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

- a review of 1 randomized controlled trial in patients with CM; 1 long-term extension study; and 1 systematic review with ITC
- patients' perspectives gathered by 2 patient groups — the Canadian Migraine Society and Migraine Canada working with Migraine Quebec

- input from public drug plans that participate in the CADTH review process
- input from 1 clinical specialist with expertise diagnosing and treating patients with CM
- input from 2 clinician groups, the Atlantic Neurology Society Group (ANSG) and the Canadian Headache Society (CHS)
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

CADTH received 2 patient-group submissions, 1 from the Canadian Migraine Society and a second from Migraine Canada and Migraine Quebec. The Canadian Migraine Society gathered data from 3 perspectives: experience from support groups with 3,200 members, personal disease experience, and email interviews with 19 patients currently taking atogepant, conducted from November 1 to December 12, 2023. The information provided by Migraine Canada and Migraine Quebec was collected through a quality-of-life online survey that was launched in late fall of 2021. In total, 1,165 adults in Canada living with migraine and their caregivers responded to the online survey. Migraine Canada launched an additional survey in November of 2023 to seek input from patients with experience with atogepant. In total, 230 adults with migraine responded to that survey.

Most of the patients from the 2 patient groups shared similar symptoms and acknowledged the impact of symptoms on their day-to-day lives and employment. The Canadian Migraine Society reported that migraine — and especially CM — affects every facet of a person's life. In the survey conducted by Migraine Canada and Migraine Quebec, the 3 outcomes reported to be most valuable to patients when trying a preventive treatment were effects on headache intensity, headache frequency, and symptoms other than pain, such as sensitivity to light and sound, nausea, and brain fog. The Canadian Migraine Society further stated that the desired outcome should be an improved quality of life.

Both groups agreed that patients with CM need access to options for effective medications (both preventive and acute), because patients with migraine may not respond similarly to the same medication or treatment. Migraine Canada and Migraine Quebec also highlighted that, considering the opioid crisis, new medications should play a role in a national plan to better manage pain and alleviate the need for opioids.

Clinician Input

The clinical expert consulted by CADTH identified several unmet needs in the treatment of CM, including poor adherence to medication, often due to common side effects, even when treatments are effective. Additionally, accessibility issues, such as the requirement for specialized administration of certain medications such as onabotulinumtoxinA, contribute to the need for treatments that are more easily accessible. The expert noted that atogepant shows promise as a first-line treatment option thanks to its

effectiveness and low side-effect profile, but cost considerations may limit its initial prescription, potentially restricting it to patients who have already tried multiple medications.

The clinical expert advised caution for patients with certain medical histories, such as stroke or cardiac disease, as well as special considerations for patients of childbearing age.

According to the clinical expert, treatment response would be assessed by reductions in headache frequency or severity. There are no standardized criteria for discontinuing an established treatment, although a minimum trial period of 6 months was recommended before considering the discontinuation of atogepant.

The clinical expert also mentioned that atogepant offers potential benefits for patients with migraine, particularly reduction in migraine and headache frequency in those with treatment-resistant or frequent EM. It can be prescribed by primary care providers without requiring specialized monitoring. However, cost considerations and the need for further research into long-term efficacy and discontinuation criteria remain significant factors in its clinical use.

Clinician Group Input

CADTH received 2 clinician group submissions from the ANSG and the CHS. The ANSG held 2 professional meetings to discuss the migraine treatment landscape, identify barriers to treatment access, and discuss the role of atogepant in fulfilling unmet patient needs on October 5 and December 18, 2023. The CHS gathered information from published clinical evidence and expert opinions from headache specialists in Canada and internationally. The ANSG identified the top 3 unmet treatment needs for migraine in Canada: adverse events (AEs) and inadequate response to acute and preventive treatments; dependence on specialists to prescribe preventive treatments; and restrictive reimbursement criteria that prevent patients' access to the care that they need. The CHS also found similar treatment gaps and some additional ones, such as the effectiveness of current available treatments wearing off, contraindications to certain drugs in some patient populations, and patients' preference for oral formulations over receiving drugs by injection. The ANSG stated that atogepant is the first oral, small-molecule CGRP antagonist approved for the preventive treatment of migraine in Canada. The CHS also commented that atogepant could be combined with drugs with a different mechanism, although evidence to support the effectiveness of such combinations is lacking. The ANSG believed that specialists, family physicians, and nurse practitioners with experience diagnosing migraine could prescribe the product and monitor the patients. The CHS further stated that prescribing atogepant should not be restricted to neurologists or specialists, since the drug is well tolerated and safe, similar to many other drugs prescribed in primary care.

Drug Program Input

Input from the drug plans identified factors pertaining to relevant comparators, considerations for initiation and discontinuation of therapy, generalizability, care provision, and system and economic considerations. CDEC weighed the body of evidence and input from the clinical expert consulted by CADTH, who 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 PROGRESS trial compared Qulipta 30 mg twice daily to 60 mg once daily to placebo over 12 weeks. There are no head-to-head comparisons of the relevant comparators in migraine prevention.	This is a comment from the drug programs to inform CDEC deliberations.
Not all plans cover Botox for migraine prevention, but some do. The place in therapy is important to clarify. Injectable CGRP inhibitor medications are listed in many jurisdictions. If needed and applicable, the initiation criteria for atogepant should be aligned with other CGRP inhibitor medications for this indication.	The committee acknowledged that applicable criteria and place in therapy will be similar to those of other CGRP inhibitors. It also added that onabotulinumtoxinA may have a slightly different place in therapy, despite evidence of effectiveness.
Considerations for initiation of therapy	
The number and type of prophylactic medications tried before initiation should be discussed. As above, the criteria for atogepant should align with other similar recommendations, if feasible.	The committee and clinical expert agreed that criteria for atogepant should be aligned with other CGRP inhibitors currently reimbursed in Canada.
Prior therapies: *Considering Botox and other CGRP inhibitor medications before initiating atogepant, how many of these (prophylactic) medications should be tried first? Can it be specified as to which medications should be tried?*	The committee acknowledged the need to consider the same listing criteria as other CGRPs. According to the clinical expert, there is no evidence for establishing a specific order of medications. For example, some patients may try onabotulinumtoxinA first because of their initial symptoms. The clinical expert mentions that any drug tried before atogepant should be included in the considerations for initiation.
Eligibility to re-treatment: Can patients be re-treated? i.e., If patients discontinue the therapy due to benefit and then relapse with symptoms, can the drug be given again? If so, what would be the appropriate timing of re-treatment?	The clinical expert, in agreement with the committee, explained that there are no compelling reasons why clinicians and patients would not consider or try this maneuver. No specific timing can be addressed with certainty, but the clinical expert would recommend observing patients during the first 3 months off therapy, which is when symptoms may come back.
Consistency with initiation criteria associated with other drugs reviewed by CADTH in the same therapeutic space: Consider alignment with other CGRP inhibitor recommendations for this indication.	The committee acknowledged the need to align criteria for atogepant with those of other CGRP inhibitors for the initiation of therapy for the indication.
Considerations for continuation or renewal of therapy	
Consistency with renewal criteria associated with other drugs reviewed by CADTH in the same therapeutic space: Consider alignment with other CGRP inhibitor recommendations for this indication.	The committee acknowledged the need to align criteria for atogepant with those of other CGRP inhibitors for the continuation or renewal of therapy for the indication.
Considerations for discontinuation of therapy	
Consider alignment with other CGRP inhibitor recommendations for this indication.	The committee acknowledged the need to align criteria for atogepant with those of other CGRP inhibitors for the discontinuation of therapy for the indication.

Implementation issues	Response
Considerations for prescribing of therapy	
In the pivotal trial, the 30 mg twice daily and 60 mg once daily dose schemes were studied. However, the 60mg once daily is the only dose recommended for this indication (based on the monograph). • *Is 30 mg twice daily an option? Other dosing options?* Is 60 mg the daily maximum dose recommended? Can it be exceeded in certain situations?	The committee and the clinical expert agreed on focusing on the 60 mg once daily dosage, as this is the accepted dosage in the Health Canada indication and in the most recent version of the product monograph. The clinical expert mentioned the lack of evidence for exceeding 60 mg daily. Hence, there is uncertainty in this regard. The clinical expert also mentioned that the 30 mg twice daily dosage is not needed in clinical practice because the 60 mg once daily dosage is more acceptable and feasible, as well as providing the same level of efficacy with easier delivery and possibly better adherence to treatment.
Consider "prescriber with experience in migraine therapy" to align with other recommendations and improve access in areas where neurologists may be difficult to access.	The committee agreed to aligning conditions for atogepant with those of other CGRP inhibitors and agreed that a prescriber with clinical experience in migraine therapy will be considered in the prescribing conditions.
Comments on *combining atogepant with Botox and possibly with other injectable CGRP inhibitor medications.*	The committee would prefer avoiding combinations. According to the clinical expert, the treating physician can combine these interventions if there is adequate, close clinical monitoring. In the clinical expert's experience, using onabotulinumtoxinA with monoclonal antibodies is common in practice. If there are no specific contraindications or drug interactions, the combination is allowed.
Generalizability	
Populations of interest match the indication but with insufficient data: Pediatric patients and patients who have tried and failed over 4 prophylactic meds – these were excluded from trial	The committee agreed that pediatric populations are out of scope for this drug, as such populations are not approved by Health Canada. Furthermore, there are insufficient data to address the use of atogepant in patients with more than 4 medications, as these were excluded from the pivotal trial. Other bodies of evidence assessing CGRP inhibitors currently reimbursed in Canada do not mention this subpopulation.
Patients on active treatment with a time-limited opportunity to switch to the drug(s) under review: If patients are currently on an injectable CGRP inhibitor, can they switch to atogepant? If yes, is there a recommended switching regimen?	The committee and clinical expert agreed that it would be feasible for patients to switch from 1 CGRP inhibitor to another, and no specific regimen would be needed to accomplish this strategy.
System and economic issues	
Presence of confidential negotiated prices for comparators: All injectable CGRP inhibitor medications for this indication and this one for the indication of episodic migraine have achieved negotiated prices.	This is a comment from the drug programs to inform CDEC deliberations.

CDEC = Canadian Drug Expert Committee; CGRP = calcitonin gene–related peptide.

Clinical Evidence

Description of Studies

One pivotal randomized controlled trial (the PROGRESS trial) was included, assessing atogepant for treatment of patients with CM. The PROGRESS study is a randomized placebo-controlled trial that assessed the effects of atogepant 60 mg once daily against placebo in adult patients with CM. The study included a subgroup of patients who have experienced an inadequate response, intolerance, or contraindication to at least 2 oral preventive migraine medications. There was a prespecified subgroup of patients with in whom 2 or more migraine prevention medications with different mechanisms of action had previously failed (N = [redacted] patients). The study assessed efficacy outcomes (MMDs, MHDs, and monthly acute medication use), function or disability outcomes (Performance of Daily Activities, missed school days or workdays, and impact of headaches on daily function), health-related quality of life, health resource utilization, and harms.

Efficacy Results

Change From Baseline in Mean MMDs

The primary efficacy end point in the PROGRESS study was the change from baseline in mean MMDs across the 12-week treatment period. In patients in whom 2 or more migraine prevention medications with different mechanisms of action had previously failed (n = [redacted]), the least squares (LS) mean change from baseline, as measured by the mean MMDs across the 12-week treatment period, was –[redacted] days (95% CI, [redacted] to [redacted] days) for atogepant 60 mg once daily compared with [redacted] days (95% CI, [redacted] to [redacted] days) for placebo. The LSMD in change from baseline in mean MMD between the 2 groups was –[redacted] days (95% CI, [redacted] to –[redacted] days; P = [redacted]), favouring atogepant 60 mg once daily.

Reduction of at Least 50% in 3-Month Average of MMDs

In the population of patients in whom 2 or more migraine prevention medications with different mechanisms of action had previously failed, the proportion of patients who had a reduction of at least 50% in the 3-month average of MMDs with atogepant 60 mg once daily was [redacted] compared with [redacted] with placebo. The adjusted absolute between-group difference was [redacted] (95% CI, [redacted] to [redacted]). The OR for the proportion of patients who demonstrated a reduction of at least 50% in the 3-month average of MMDs was [redacted] (95% CI, [redacted] to [redacted]; P = [redacted]), favouring atogepant 60 mg once daily.

Change From Baseline in Mean MHDs

In the population of patients in whom 2 or more migraine prevention medications with different mechanisms of action had previously failed, the LS mean change from baseline in the number of mean MHDs across the 12-week treatment period was [redacted] days (95% CI, [redacted] to [redacted] days) with atogepant 60 mg once daily compared with [redacted] days (95% CI, –[redacted] to [redacted] days) with placebo. The LSMD in change from baseline between the 2 groups was [redacted] days (95% CI, [redacted] to [redacted] days; P = [redacted]), favouring atogepant 60 mg once daily.

Change From Baseline in Mean Monthly Days of Acute Medication Use

In the population of patients in whom 2 or more migraine prevention medications with different mechanisms of action had previously failed, the LS mean change from baseline in the mean number of days of acute

medication use across the 12-week treatment period was [redacted] for atogepant 60 mg once daily compared with [redacted] with placebo. The LSMD in change from baseline in mean number of days of acute medication use between atogepant 60 mg once daily and placebo was [redacted], favouring atogepant 60 mg once daily.

Change From Baseline in Mean Monthly Performance of Daily Activities Domain Score of the Activity Impairment in Migraine–Diary

In the population of patients in whom 2 or more migraine prevention medications with different mechanisms of action had previously failed, the LS mean change from baseline in the mean monthly Performance of Daily Activities domain score of the Activity Impairment in Migraine–Diary (AIM-D) measure across the 12-week treatment period was [redacted] for atogepant 60 mg once daily compared [redacted] for placebo, where negative values imply improvements from baseline. The LSMD in change from baseline in mean monthly Performance of Daily Activities domain score of AIM-D across the 12-week treatment period between the 2 groups was [redacted], favouring atogepant 60 mg once daily.

Change From Baseline in the Migraine Disability Assessment Total Score

This end point was not available for the population of patients in whom 2 or more migraine prevention medications with different mechanisms of action had previously failed. Hence, it was assessed only in the overall modified intention-to-treat (mITT) population, where the LS mean change from baseline in the Migraine Disability Assessment (MIDAS) total score at week 12 was [redacted] for atogepant 60 mg once daily (improvement) as compared with [redacted] with placebo. The LSMD in change from baseline between the 2 groups was [redacted], favouring atogepant 60 mg once daily.

Change From Baseline in Headache Impact Test Total Score

In the population of patients in whom 2 or more migraine prevention medications with different mechanisms of action had previously failed, the LS mean change from baseline in the Headache Impact Test (HIT-6) total score at week 12 [redacted] for atogepant 60 mg once daily (negative numbers implying improvement) and [redacted] in the placebo group. The LSMD in change from baseline between the 2 groups was [redacted], favouring atogepant 60 mg once daily.

Change From Baseline in Migraine-Specific Quality of Life Questionnaire Role Function Restrictive Domain Score

In the population of patients in whom 2 or more migraine prevention medications with different mechanisms of action had previously failed, the LS mean change from baseline in Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) Role Function Restrictive domain score at week 12 was [redacted] higher for atogepant 60 mg once daily, while the placebo group had an increase of [redacted], where higher values suggest an improvement in patients' functioning in daily social and work-related activities. The LSMD in change from baseline in mean monthly MSQ v2.1 Role Function Restrictive Domain Score at week 12 between the 2 groups was [redacted] in the atogepant 60 mg once daily group when compared with placebo.

Change From Baseline in Percent Work Time Missed Assessed by the Work Productivity and Activity Impairment Questionnaire: Migraine

This was only evaluated in subset of the overall (mITT) population, and no information was provided for the subgroup of patients in whom 2 or more migraine prevention medications with different mechanisms of action had previously failed. In the overall (mITT) population, the LS mean change from baseline in the percent work time missed, assessed with the Work Productivity and Activity Impairment (WPAI) questionnaire: Migraine at week 12 was [redacted]) for atogepant 60 mg once daily (negative values imply improvement) compared with [redacted]) with placebo. The LSMD in change from baseline in percent work time missed at week 12 was −4.85 points (95% CI, −9.48 to −0.23 points; P = 0.0397), favouring atogepant 60 mg once daily.

Harms Results

The most frequently reported AEs (5% or more of patients in the safety population) in the atogepant treatment group were constipation (10%) and nausea (9.6%). In the population of patients in whom 2 or more migraine prevention medications with different mechanisms of action had previously failed, patients also experienced [redacted].

In the population of patients in whom 2 or more migraine prevention medications with different mechanisms of action had previously failed, [redacted] of patients in the atogepant 60 mg once daily treatment group and [redacted] of patients in the placebo treatment group. [redacted] of patients in the atogepant 60 mg once daily treatment group, and [redacted] of patients in the placebo treatment group. [redacted] of patients in the atogepant 60 mg once daily treatment group, and [redacted] of patients in the placebo treatment group.

[redacted]

AEs leading to treatment discontinuation were infrequent in the atogepant 60 mg once daily treatment group and placebo group, [redacted]. All AEs leading to treatment discontinuation in the atogepant 60 mg once daily group occurred in fewer than 1% of patients.

No deaths were reported in the PROGRESS trial.

AEs of special interest were reported at low rates. [redacted]. A total of 3 patients had an elevated alanine aminotransferase or aspartate aminotransferase laboratory value that was 3 × the upper limit of normal or higher, which were subject to blinded adjudication by the Adjudication Committee.

Critical Appraisal

The PROGRESS trial is a randomized controlled trial investigating the efficacy and safety of atogepant 60 mg once daily (the dosage of interest for this review) compared with placebo. The study involved a randomization and allocation concealment process that was judged to be properly implemented, ensuring an overall balanced distribution of participants to the atogepant 60 mg once daily or placebo arms. The number

of prior migraine prevention medications failed was a stratification factor in the randomization, which should ensure that the randomization is upheld in the subgroup of patients in whom 2 or more migraine prevention medications with different mechanisms of action had previously failed. Some minor baseline imbalances were observed for the WPAI end point, obtained from a subset of the population, with imbalances between groups. However, these imbalances were judged to present a low risk for introducing bias or for suggesting problems in the randomization process. In the study, patients maintained good adherence to the intended intervention. Concomitant medication use was comparable across the placebo and atogepant 60 mg once daily treatment groups.

The subgroup of patients in whom 2 or more migraine prevention medications with different mechanisms of action had previously failed, which represents [redacted] (n = [redacted]) of the total mITT population, is of interest for this CADTH report because it is the focus of the sponsor's reimbursement request. However, the sample size (power) calculation did not consider this subgroup separately. Therefore, it is unknown whether there was enough statistical power to detect any differences in treatment effect between the intervention and comparator arms in this subgroup. However, greater effect sizes for the subgroup of patients in whom 2 or more migraine prevention medications with different mechanisms of action had previously failed were consistent across all key clinical end points (change from baseline in MMDs, MHDs, days of medication use, reduction of at least 50% in 3-month average MMDs) compared with the mITT population. There were no instances of meaningful missing outcome data, except for [redacted] patients in the atogepant 60 mg and [redacted] in the placebo group for the main outcomes in the mITT population, which was unlikely to significantly affect the results. In the PROGRESS study, measurements of the outcomes were appropriate. The blinding of participants and clinical investigators was kept throughout the conduct of the study, and there is no evidence that patients or personnel became unblinded. The results were reported in accordance with predefined protocols, including the results from the subgroup of patients in whom 2 or more migraine prevention medications with different mechanisms of action had previously failed, reducing the likelihood of selective reporting bias.

Overall, the study appears to have minimized risks across all domains assessed for risk of bias for the outcomes addressed when comparing atogepant with placebo.

GRADE Summary of Findings and Certainty of the Evidence

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

Following the GRADE approach, evidence from randomized controlled trials start as high-certainty evidence but can be rated down if there are concerns about study limitations (internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effect estimates, and publication bias.

When possible, certainty is rated in the context of the presence of an important effect (i.e., how certain are we that the effect is a nontrivial treatment effect?). To determine whether an effect is important, GRADE suggests using thresholds of clinical importance (minimal important difference [MID]). If a threshold is not

possible to obtain, the certainty is rated in the context of the presence of any treatment effect (i.e., how certain are we that there is any — beneficial or harmful — effect?). In this case, the clinical importance of any effect remains unclear. In all cases, the assessment of certainty of evidence is based on the point estimate of each outcome and where it is located relative to the chosen threshold for a clinically important effect (when a threshold is available) or to the null (when there is no threshold).

A GRADE summary of findings for the body of evidence for this review included the evaluation of the main outcomes considered important by clinicians, patient groups, and stakeholders. These assessments are presented in Table 3 for each outcome included.

Table 3: Summary of Findings for Atogepant 60 mg Once Daily Versus Placebo for Patients With Chronic Migraine and 2 or More Treatment Failures

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Atogepant 60 mg	Difference		
Migraines, headaches, and acute medication use							
LS mean change from baseline in MMDs Follow-up: 12 weeks	(1 RCT)	NA		)	fewer (fewer)	Moderate[a]	Atogepant 60 mg once daily likely results in a clinically important reduction in the mean MMDs when compared with placebo.
Reduction of ≥ 50% of 3-month MMDs Follow-up: 12 weeks	(1 RCT)	OR = ( )	per 1,000	per 1,000 (NR)	more per 1,000 (more per 1,000)	Moderate[a]	Atogepant 60 mg once daily likely results in an increase in the proportion of patients achieving a ≥ 50% reduction in MMDs when compared with placebo. There is uncertainty about the clinical importance of the increase.
LS mean change from baseline in MHDs Follow-up: 12 weeks	(1 RCT)	NA		( )	fewer (fewer)	Moderate[a]	Atogepant 60 mg once daily likely results in a clinically important reduction in mean MHDs when compared with placebo.
LS mean change from baseline in monthly days of acute medication use Follow-up: 12 weeks	(1 RCT)	NA		( )	fewer (fewer)	Moderate[a]	Atogepant 60 mg once daily likely reduces the monthly days of acute medication use when compared with placebo. There is uncertainty about the clinical importance of the reduction.
Function or disability							
LS mean change from baseline in mean monthly Performance of Daily Activities domain score of	(1 RCT)	NA			lower points (lower)	Moderate[b]	Atogepant 60 mg once daily likely reduces (improves) the monthly Performance of Daily Activities score of the AIM-D when compared

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Atogepant 60 mg	Difference		
the AIM-D (0 [best] to 100 [worst]), points Follow-up: 12 weeks							with placebo. There is uncertainty about the clinical importance of the improvement.
LS mean change from baseline in MIDAS total score (0 [no disability] to > 40 [very severe disability]), points Follow-up: 12 weeks	(1 RCT)	NA			lower points (lower to lower)	Moderate[c,d]	Atogepant 60 mg once daily likely reduces (improves) in the MIDAS total score when compared with placebo. There is uncertainty about the clinical importance of the improvement.
LS mean change from baseline in Headache Impact Test (HIT-6) total score (36 [best] to 78 [worst]), points. Follow-up: 12 weeks	(1 RCT)	NA			lower (to lower)	Moderate[a,e]	Atogepant 60 mg once daily likely results in a clinically important reduction (improvement) in the impact of headaches in daily function as measured by the HIT-6 scale, when compared with placebo.
HRQoL							
LS mean change from baseline in monthly MSQ v2.1 (RFR domain) (0 [worst] to 100 [best]), points Follow-up: 12 weeks	(1 RCT)	NA			higher to higher)	Moderate[a,f]	Atogepant 60 mg once daily likely results in a clinically important increase in HRQoL (work-related and daily social activities) when compared with placebo.
Resource utilization							
Change from baseline in percent worktime missed: (WPAI: Migraine) (0% [best] to 100% [worst]), % Follow-up: 12 weeks	(1 RCT)	NA			| lower (lower to higher)	Low[g,h]	Atogepant 60 mg once daily may reduce the percent worktime missed. The clinical relevance of the effect size is unclear.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Atogepant 60 mg	Difference		
Harms							
AEs, SAEs, WDAEs, deaths Follow-up: 12 weeks	[redacted] (1 RCT)	NA	AEs were overall similar [redacted] Only [redacted] was deemed numerically increased in atogepant [redacted] versus placebo [redacted] SAEs were reported by [redacted] in the atogepant group and [redacted] in the placebo group. WDAEs were reported in [redacted] in each group. No deaths were reported in any group.			Moderate[a]	Atogepant 60 mg once daily likely results in little to no difference in AEs, SAEs, and WDAEs. Atogepant likely increases the number of mild/ moderate constipation cases; the clinical importance is uncertain.

AE = adverse event; AIM-D = Activity Impairment in Migraine–Diary; CI = confidence interval; HIT-6 = Headache Impact Test; HRQoL = health-related quality of life; LS = least squares; MHD = monthly headache day; MIDAS = Migraine Disability Assessment; MMD = monthly migraine day; MSQ v2.1 = Migraine-Specific Quality of Life Questionnaire version 2.1; NA = not applicable; NR = not reported; OR = odds ratio; RCT = randomized controlled trial; RFR = Role Function Restrictive; SAE = serious adverse event; WDAE = withdrawal due to adverse events; WPAI = Work Productivity and Activity Impairment.

Note: Analyses are unadjusted for multiplicity. The absolute difference (95% CI) in the change from baseline in reduction of at least 50% in the 3-month average of MMDs was requested from the sponsor for interpretation purposes.

[a]Rated down 1 level for imprecision. The population is composed by those patients with the reimbursement criteria (2 or more treatment failures); the sample size and optimal information size for this subgroup was not reached. One day was defined as the threshold for a small but important benefit (or harm) for the change from baseline in MMDs. For AEs, the number of events was small.

[b]Rated down 1 level for imprecision. No MID is available for this measure; therefore, the effect was judged versus the null. The optimal information size (OIS) was not reached, but sample size is more than 30% of the OIS.

[c]The information was obtained from the overall population of patients in whom 2 or more migraine prevention medications with different mechanisms of action had previously failed. Within-group MID (change from baseline) is estimated to be 4.5 points.

[d]Rated down 1 level for imprecision.

[e]Within-patient and between-group MID for patients with CM is estimated to be 6 points and 2.3 points, respectively.

[f]Within-group MID is estimated to be 11 points. A lenient threshold of 5.5 points would not lead to rating down for imprecision; however, the OIS is not reached, and the imprecision will remain rated down 1 level.

[g]Rated down 1 level for imprecision. The 95% CI excludes the null but may include an important benefit and a trivial effect. Since there is no threshold of between-group clinical importance, the clinical relevance of the effect remains unclear. Furthermore, the sample size on this outcome did not reach the OIS.

[h]Rated down 1 level due to risk of bias, as this outcome was assessed in a subset of the target population; prognostic balance is not ensured.

Long-Term Extension Studies

Description of Studies

Study 3101-312-002 (Study 312) is a multicentre, open-label, 156-week, long-term safety extension study conducted in all eligible patients who completed the PROGRESS study or ELEVATE study. The ELEVATE study was a phase III, multicentre, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of oral atogepant for the prevention of migraine in participants with EM in whom 2 to 4 classes of oral preventive treatments had previously failed. Study 312 consists of a 156-week open-label treatment period and a safety follow-up period of 4 weeks. The primary objective of the study is to assess the safety and tolerability of long-term use of atogepant 60 mg once daily treatment in patients with CM or EM. Efficacy end points for long-term evaluation were included; however, were they considered exploratory. An interim analysis (November 2023) is presented here, including only patients from the PROGRESS study. Patients were instructed to take atogepant 60 mg orally at approximately the same time each day for 156 weeks. Patients were followed for 4 weeks following completion or discontinuation of atogepant. All analyses were performed for the full population in the extension study, and no analyses were presented specific to the population of patients in whom 2 or more migraine prevention medications with different mechanisms of action had previously failed.

Efficacy Results

Overall, reductions in mean MMDs, mean MHDs, and mean monthly days of acute medication use relative to the lead-in study baseline were observed during the open-label treatment period. The proportion of patients with at least a 50% improvement in MMDs was 41.0% across the 12-week treatment period in the PROGRESS study, increased to 67.0% for weeks 13 to 16, and remained similar for weeks 29 to 32 and 45 to 48. The change from baseline in monthly Performance of Daily Activities domain score of the AIM-D remained relatively consistent across weeks 13 to 16, weeks 29 to 32, and weeks 45 to 48. Moreover, the change from baseline in the MSQ v2.1 Role Function Restrictive domain score at weeks 12, 20, 28, 36, 44, and 52 remained similar.

Harms Results

At the time of the interim analysis, [redacted] of patients had completed the study and [redacted] were still continuing. Of the 325 patients enrolled in Study 312 from the PROGRESS trial, [redacted] discontinued treatment, with [redacted] being the most common reason for discontinuation. Treatment-emergent AEs were reported by 265 patients (81.5%). The most commonly reported AEs included COVID-19 (30.8%), constipation (10.2%), nasopharyngitis (9.8%), urinary tract infection (6.2%), and insomnia (5.5%). Serious AEs (SAEs) were reported by 20 (6.2%) patients. The following SAEs were reported by 1 patient each: [redacted]. AEs leading to study drug discontinuation were reported in 27 patients (8.3%) and included: [redacted]

Critical Appraisal

Study 312 was limited by its open-label and noncomparative design; since there is no comparator, it cannot be confirmed whether the results observed are attributable to the effects of the drug or to the natural history of the condition. Furthermore, the mITT population analyzed excluded [redacted] of patients. The large missing outcome data (more than [redacted]) introduces a risk of bias. The open-label and nonblinded nature of the study increases the risk of bias. Because the outcome measures are generally self-reported, they are subjective, and it is uncertain whether they could be replicated in another population beyond that included in the study. No information was provided on the population of patients in whom 2 or more migraine prevention medications with different mechanisms of action had previously failed (the population considered in this reimbursement request). It is therefore impossible to know whether the effects observed in the full population would be similar in that group. Because the patients who took part in the open-label long-term safety extension phase were originally from the pivotal PROGRESS trial, it is reasonable to expect that the same limitations to generalizability are relevant to the open-label long-term safety extension phase. Given the nature of noncomparative study design, it is impossible to compare the effectiveness and tolerability of atogepant as preventive treatment of CM with other preventive treatment.

Indirect Comparisons

Description of Studies

The ITC submitted is a network meta-analysis (NMA) conducted by the sponsor. The objective of the NMA was to evaluate the efficacy, safety, and tolerability of atogepant compared with other CGRP inhibitors, i.e., the comparators of interest that are approved medications for the treatment of CM in Canada (atogepant, onabotulinumtoxinA, eptinezumab, erenumab, fremanezumab, and galcanezumab).

A clinical systematic literature review was performed using the population, interventions, comparators, outcomes, and study design criteria previously established for the reimbursement request. [redacted].

Efficacy Results

Baseline characteristics of patients (age, sex, race) involved in all comparisons were overall similar across studies. [redacted] These wide CrIs denote imprecise estimates for any comparison of atogepant 60 mg once daily with all active treatments. These wide CrIs were observed whether the analysis was made in the fixed effects or random effects models.

[redacted]

[redacted]

[redacted] The effect estimates had wide CrIs (imprecision), which conveyed important uncertainty, limiting the ability to draw definite conclusions for these comparisons.

Harms Results

In the evidence from the NMA, only the overall CM population was assessed for harms. In this, [redacted]

For the rest of the comparisons, the hazard ratios were also accompanied by wide CrIs, which conveyed uncertainty due to imprecision in the hazard rates between atogepant and all relevant comparators.

Critical Appraisal

The systematic review and NMA aimed to evaluate the efficacy and harms of atogepant 60 mg once daily compared with relevant comparators for CM treatment, based on drugs licensed and approved in Canada. While relevant trials for the specific population and comparators were appropriately identified and included, details regarding the screening process were lacking. Despite well-described study designs, there was a notable absence of information on data extraction and risk of bias assessment procedures. Some head-to-head trials were excluded due to strict criteria. To address this, a sensitivity analysis was conducted to address effects based on excluded populations. This ensures the robustness in the final estimates. Some differences, however, were observed between fixed effects and random effects models, implying possible inconsistencies among the included trials.

The construction of networks was thorough, assessing model fit, consistency, convergence, and heterogeneity; establishing comparability among populations included in each network; and upholding the transitivity assumption. However, there was no formal assessment of publication bias, and imprecise effect estimates for several end points posed challenges in drawing definitive conclusions.

Overall, the populations in individual studies were deemed generalizable to the Canadian population, with no significant concerns regarding the applicability of the results detected. However, the NMA did not include several relevant outcomes of interest (e.g., MIDAS, HIT-6, MSQ, WPAI, SAE). Also, relevant to this submission, there was a short length of follow-up, precluding long-term assessments required for rare AEs and efficacy beyond 24 weeks. The lack of comparison with eptinezumab was considered important in the Canadian landscape, as were the few comparisons available for the population of patients in whom 2 or more migraine prevention medications with different mechanisms of action had previously failed.

Overall, the systematic review and NMA effectively synthesized existing evidence; however, some methodological gaps and imprecisions in effect estimates warrant cautious interpretation of the findings.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Information

Component	Description
Type of economic evaluation	Cost-minimization analysis
Target population	Adults with > 15 headache days per month (among which 8 days are considered to be migraine days) and who have previously failed to respond, are intolerant, or have a contraindication to, at least 2 migraine preventive therapies
Treatment	Atogepant 60 mg[a]
Dosage regimen	60 mg once daily
Submitted price	$18.44 per 60 mg tablet
Submitted treatment cost	$6,735 per patient per year
Comparators	• Fremanezumab • Galcanezumab • Eptinezumab • OnabotulinumtoxinA (scenario only)
Perspective	Canadian publicly funded health care payer
Time horizon	5 years
Key data sources	Network meta-analysis, with the effectiveness of atogepant informed by the PROGRESS trial
Costs considered	Drug acquisition, drug administration, health care resource use
Key limitations	• The clinical effectiveness of atogepant compared to other preventive migraine treatments is uncertain. There is a lack of direct head-to-head evidence comparing atogepant to CGRP inhibitors and there is high uncertainty in the results of the sponsor's submitted NMA, owing to wide credible intervals that include effect estimates both in favour of and against atogepant compared to other treatments in the reimbursement population. • The timing of assessment of initial treatment response in the sponsor's model is not aligned with clinical practice or with public drug plan renewal criteria for CGRP inhibitors reimbursed for CM. Clinical expert feedback obtained by CADTH indicated that assessment of initial response to treatment would be after a 6-month trial, not 3 months, as assumed by the sponsor. There is a lack of comparative clinical evidence at 6 months to support clinical similarity of atogepant to other reimbursed treatments for CM. • The exclusion of onabotulinumtoxinA from the sponsor's base case was inappropriate, based on clinical expert input received by CADTH and its reimbursement for CM in some CADTH-participating drug plans. • The submitted model structure does not adequately reflect the management of migraine in clinical practice, in that the cost of subsequent therapies was excluded by the sponsor. The magnitude of impact of this limitation on the estimated costs of treatment is unknown. • Confidential pricing agreements exist for eptinezumab, fremanezumab, and galcanezumab for the prevention of migraine. As such, the cost paid by the participating drug plans for comparators may be

Component	Description
	less than assumed by the sponsor, and the submitted price of atogepant may require a price reduction to avoid incurring additional costs relative to its comparators.
CADTH reanalysis results	• In the CADTH base case, CADTH included onabotulinumtoxinA as a comparator. Results of this analysis suggest that atogepant is associated with higher costs compared to onabotulinumtoxinA (incremental cost: $2,479) and lower costs compared to eptinezumab, galcanezumab, and fremanezumab (range of incremental savings: $15 to $741 per patient). The differences in costs were mainly attributed to differences in drug acquisition costs. • CADTH could not address uncertainty in the clinical evidence, the timing of response assessment, exclusion of costs related to subsequent treatments, and confidential pricing agreements for comparators. Thus, whether the reimbursement of atogepant will be cost-saving compared to currently reimbursed treatments for CM is uncertain. Reimbursement of atogepant may lead to additional costs to the health care system.

CM = chronic migraine.

[a]Atogepant is also available as 10 and 30 mg oral tablets. These strengths were not submitted to CADTH as part of the current review of atogepant for the prevention of CM.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis:

- The exclusion of onabotulinumtoxinA from the sponsor's base case was inappropriate, given that onabotulinumtoxinA is used in the requested reimbursement population as part of standard of care and is funded in some jurisdictions.
- The NIHB population was inappropriately calculated.
- The price of drugs paid by public plans is uncertain, as confidential pricing is likely in place.

In the CADTH base case, onabotulinumtoxinA was included as a comparator in jurisdictions where it is funded for the reimbursement population (i.e., Alberta, Ontario). In this analysis, the budget impact of reimbursing atogepant for the prevention of CM in adults who have previously failed to respond, are intolerant to, or have a contraindication to at least 2 migraine preventive therapies is expected to result in a savings of $994,373 over 3 years (year 1: $235,229, year 2: $340,637, year 3: $418,507).

Uncertainty remains in the prices paid by public plans for comparators. The presence of confidential prices for comparators may result in the cost savings realized by the drug plans being lower than predicted by the sponsor's and CADTH's base case.

All stakeholder feedback received in response to the draft recommendation is available on the CADTH website.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Danyaal Raza, Dr. Edward Xie, and Dr. Peter Zed.

Meeting date: May 22, 2024

Regrets: One expert committee member did not attend.

Conflicts of interest: None.

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