CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

Final

Fremanezumab (Ajovy)

Indication: Prevention of migraine

Recommendation: Reimburse With Conditions

This document was initially posted on March 26, 2021 and subsequently revised on April 1, 2021 to correct an error in the annual prices of the comparator drugs and to remove a discussion point.

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Single Technology

What is the CADTH reimbursement recommendation for Ajovy?

CADTH recommends that Ajovy (fremanezumab) should be reimbursed by public drug plans for the prevention of episodic and chronic migraines if certain conditions are met.

What are the conditions for reimbursement?

Ajovy should only be reimbursed if the price is reduced by 61% to 71%

Which patients are eligible for coverage?

Ajovy should only be covered in adults to prevent episodic or chronic migraines if the patient doesn't respond to at least two oral migraine medications.

Why did CADTH make this recommendation?

Evidence from three clinical trials demonstrated that Ajovy reduced the mean number of days patients experienced migraines and headaches per month compared with placebo. Ajovy also reduced disability associated with migraines. At the submitted price, Ajovy is not cost-effective.

Key Messages

- The totality of clinical evidence suggests that Ajovy should be reimbursed to prevent episodic and chronic migraines in adults who fail to respond to at least two oral medications.
- The price of Ajovy would need to be reduced by 61% to 71% to be cost-effective.
- If the price of Ajovy is not reduced to a point that is affordable to public payers, there may be delays in providing this treatment to eligible patients with migraine. However, there are other alternative treatments available for migraine prevention.

What is migraine?

Migraine is a neurological disease in which people experience recurrent attacks of pulsating headache pain of at least moderate severity. Migraines may be episodic or chronic. Migraine is considered a common disease, affecting at least 2.6 million adult women and 1 million adult men in Canada. Patients may need to try several drug therapies to prevent migraines because of a lack of effectiveness or intolerable adverse effects.

What is Ajovy?

Ajovy is approved by Health Canada for the prevention of migraine in adults who have had at least four migraine days monthly. It is a medication (antibody) that stops the effects of a protein called calcitonin gene-related peptide (CGRP) from causing inflammation and pain in the nervous system of people who have migraines.

How much does Ajovy cost?

Treatment with Ajovy is expected to cost approximately $7,020 per patient per year.

What other drugs are available for migraine prevention?

There are other drugs available for preventing migraines, including other CGRP blockers, beta blockers, antidepressants, and anti-seizure drugs.

Unmet Needs in migraine prevention

Most of the currently available medications for the prevention of migraine are not specifically approved for this use, are associated with numerous adverse effects that patients with migraine find difficult to tolerate. Despite several available medications, there remains a need for drugs that are effective in preventing migraines and with minimal adverse effects.

How much do other treatments cost?

Aimovig, Botox, amitriptyline, propranolol, and topiramate cost $6,384, $3,105, $32 to $169, $89 to $149, and $167 respectively, per patient per year.

CADTH

FREMANEZUMAB (AJOVY – TEVA CANADA INNOVATION)

Therapeutic Area: Prevention of migraine

Recommendation

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

Rationale for the Recommendation

Three randomized controlled trials (RCTs) (HALO EM, HALO CM, FOCUS) demonstrated that fremanezumab reduced mean monthly migraine days (MMD) and average number of headache days from baseline compared to placebo after 12 weeks in patients with chronic migraine and episodic migraine. The treatment groups who received fremanezumab had a reduction in MMDs of 1 to 2 days in the HALO trials and 3.1 to 3.5 days in the FOCUS trial when compared with those who received placebo. Disability scores as measured by the six-item headache impact test (HIT-6) and the migraine disability assessment (MIDAS) improved for fremanezumab treatment groups in patients with chronic migraine and episodic migraine, respectively. Outcomes related to work and daily life, as well as health-related quality of life were numerically improved in the fremanezumab treatment groups. No safety or tolerability issues emerged from the three RCTs. Although the clinical significance of the differences observed versus placebo are difficult to determine because there is no established minimally important difference (MID) for many of the outcome measures, such as the change in MMD, number of headache days, and the MIDAS, CDEC concluded the totality of the submitted evidence established the therapeutic relevance of fremanezumab as a preventive therapy for migraines in adults.

The sponsor's submitted price of fremanezumab is $585 per single-dose pre-filled syringe (225 mg). The average daily cost is $19.22 and the average annual cost of treatment with is $7,020 per patient, which is higher than the annual publicly available cost for other medications commonly used to prevent migraines. Although the cost-effectiveness of fremanezumab is uncertain due to limitations in the data available to assess the comparative effectiveness of fremanezumab to other therapies used to prevent migraine, fremanezumab was not cost-effective compared to best supportive care (BSC) at a $50,000 per quality-adjusted life-year (QALY) willingness-to-pay (WTP) threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason
Initiation	
1. The patient has a confirmed diagnosis of episodic or chronic migraine according to the International Headache Society criteria, defined as: 1.1. Episodic migraine: migraine headaches on at least 4 days per month and less than 15 headache days per month for more than 3 months. 1.2. Chronic migraine: headaches for at least 15 days per month for more than 3 months of which at least eight days per month are with migraine.	HALO EM and HALO CM enrolled patients with episodic migraine and chronic migraine, respectively. FOCUS included a mixed population of patients with episodic or chronic migraine. All three RCTs provided evidence that fremanezumab is superior to placebo in reducing the mean MMDs and average number of headache days in patients with episodic migraine and chronic migraine.
2. The patient has experienced an inadequate response, intolerance, or contraindication to at least two oral prophylactic migraine medications.	The FOCUS trial included adults with episodic migraine or chronic migraine who had documented inadequate response to at least 2 classes of prior preventive treatment.
3. The physician must provide the number of headache and migraine days per month at the time of initial request for reimbursement.	See Initiation Condition 1 and Renewal Condition 1.
4. The maximum duration of initial authorization is six months.	Although the RCTs measured outcomes at 12 weeks, authorization of funding for 6 months provides flexibility to accommodate the practical challenges of assessing clinical response after 3 months of treatment. The 6-month-long maximum duration of authorization is also consistent with the duration recommended for other migraine prophylactic medications reviewed previously by CDEC.
Renewal	
1. The physician must provide proof of beneficial clinical effect when requesting continuation of reimbursement, defined as a reduction of at least 50% in the average number of migraine days per month at the time of first renewal compared with baseline. At subsequent renewals the physician must provide proof that the initial 50% reduction in the average number of migraine days per month has been maintained.	A 50% reduction in the number of MMDs was a pre-defined secondary end point in each of the included RCTs.
2. The maximum duration of subsequent authorizations following the initial authorization is six months.	See Initiation Criterion 4.
Prescribing	
1. The patient should be under the care of a physician who has appropriate experience in the management of patients with migraine headaches.	Accurate diagnosis of migraine is important to ensure that fremanezumab is prescribed to the appropriate patients. In addition, several migraine prophylaxis treatment options must be considered when selecting the most appropriate therapy for patients who are refractory to one or more first-line options.
Pricing	
1. A reduction in price	Fremanezumab is more costly than BSC in all patient subgroups (episodic or chronic migraine), regardless of number of prior preventive migraine therapies (< 2, ≥2). A price reduction of 61% to 71% would be required for fremanezumab to be considered cost-effective compared to BSC at a WTP threshold of $50,000 per QALY.

Implementation Guidance

- Inadequate response to oral prophylactic therapies is defined as less than a 30% reduction in frequency of headache days to an adequate dose and duration of at least two prophylactic medications, which must be of a different class.
- Oral prophylactic therapies to be considered include:
  - beta blockers
  - tricyclic antidepressants
  - verapamil or flunarizine
  - sodium valproate (or divalproex sodium)
  - topiramate
  - gabapentin
- A list of previously tried oral prophylactic medications, including doses and duration, and reasons for discontinuance, should be provided by the requesting physician.
- At least one of the two prophylactic medications previously used must have been discontinued because of lack of therapeutic effectiveness.
- Some jurisdictions may want to include a reduction of at least 30% in the number of headache days per month and an improvement of at least five points in the HIT-6 score, compared with baseline, as an alternative criterion for renewal of reimbursement. Jurisdictions that choose to include this criterion should also request that the physician provide the score obtained on the HIT-6 at the time of initial request for reimbursement.
- The sponsor-provided pharmacoeconomic model compared the cost-effectiveness of fremanezumab with onabotulinum toxin A (OnaA) and erenumab, only in the patient population with chronic migraine. Therefore:
  - If either OnaA or erenumab are reimbursed for the prevention of chronic migraine, then the cost of fremanezumab should not exceed the cost of the least costly of these (OnaA or erenumab).
  - If OnaA or erenumab are not reimbursed for the prevention of chronic migraine, a price reduction would be required to increase the likelihood that fremanezumab is cost-effective.
- Fremanezumab should not be used in combination with OnaA.

Discussion Points

- Migraine is a common and debilitating neurologic disease that may lead to poor quality of life, social isolation, and an inability to participate in daily activities. CDEC discussed patient and clinician input that current prophylactic medications do not benefit everyone with migraine and have adverse effects that may make them difficult to tolerate, leading to poor adherence and non-achievement of desired outcomes.
- The high selectivity of the populations based on restrictive eligibility criteria of the included studies may restrict generalizability to the general migraine population. None of the included patients had received a recent trial (within the previous 3 to 4 months) of OnaA.
- Data are lacking from high-quality studies to estimate the effect of fremanezumab on outcomes important to patients, including functionality, regaining active work and personal life roles, and reducing frequency of emergency department visits.
- CDEC noted the lack of evidence regarding combination use of fremanezumab with OnaA and other medications used for prevention of migraines is an important gap in evidence.
- Comparative evidence was limited to indirect treatment comparisons of fremanezumab with other medications used to prevent migraines. The limitations with the indirect evidence, such as the small size and sparse networks, mean there were no statistically robust analyses to determine the comparative effects of fremanezumab.

Background

Fremanezumab has a Health Canada indication for the prevention of migraine in adults who have had at least four migraine days monthly. Fremanezumab is a fully-humanized monoclonal antibody that binds to and inhibits the CGRP receptor, which has been implicated in the pathophysiology of migraine based on CGRP's vascular effects and the effects on transmission of pain signals in the central nervous system. It is available as subcutaneous injection and the Health Canada–approved doses are 225 mg (1 subcutaneous injection) once a month or 675 mg (3 separate subcutaneous injections of 225 mg one after another) every 3 months.

Summary of Evidence

To make their recommendation, CDEC considered the following information:

- The CADTH clinical review that included a systematic review which included three phase III RCTs, an appraisal of two indirect comparisons (one provided by the sponsor), and a review of longer-term study data.
- Patients' perspectives gathered by one patient group input submission, which was a joint effort between Migraine Canada and Migraine Quebec.
- One clinical specialist with expertise in diagnosing and treating patients with migraines.
- The CADTH appraisal of the pharmacoeconomic model submitted by the sponsor.

Summary of Patient Input

One patient group submission made jointly between Migraine Canada and Migraine Quebec provided input for this review. Patient perspectives were obtained primarily through online and in person surveys. The following is a summary of key input from the perspective of the patient groups.

Migraines are common and can have a significant impact on patients' lives and the lives of those around them. During attacks, the ability to accomplish tasks, work, and interact with others is compromised. Cognition is affected, with slowed thinking, lack of focus, and difficulty in reading and speaking. Patients report having been disabled as a result of migraines, unable to work, and dependent on others for many activities of daily living.

Patients often try multiple medications with no success, or experience side effects and seek alternative therapies.

Patients often experience side effects from therapies. These include sleepiness, fatigue, weight gain, gastrointestinal upset, depression, anxiety or mood difficulties, dizziness, cognitive problems, low blood pressure, fainting, and exercise intolerance. These are frequently problematic enough to lead to the discontinuation of medication.

For patients, the most important aspect of a treatment is efficacy (reducing the frequency, severity and duration of migraines), followed by reduced side effects and improved quality of life.

Clinical Trials

The CADTH systematic review included three phase III, multinational, double-blind, RCTs of patients with chronic migraine and patients with episodic migraine, funded by the sponsor. No active comparator trials were identified for the review. HALO CM (N = 1,130) was conducted in patients with chronic migraine and HALO EM (N = 875) was conducted in patients with episodic migraine. Both studies randomized patients to fremanezumab monthly (chronic migraine: 675/225/225 mg; episodic migraine: 225/225/225 mg), quarterly (675 mg/placebo/placebo mg), and placebo with a 12-week double-blind treatment period. The FOCUS study (N = 838) included a mix of patients with chronic migraine or episodic migraine who were randomized to fremanezumab monthly (chronic migraine: 675/225/225 mg; episodic migraine: 225/225/225 mg), quarterly (675 mg/placebo/placebo), or placebo. FOCUS included a double-blind 12-week treatment period, followed by a 12-week open-label period, with patients followed for up to 46 weeks.

The high selectivity of the study population based on a stringent list of eligibility criteria of the included studies may restrict generalizability to the general migraine population. All three studies excluded patients who had received OnaA (for migraine or other

indication) within the previous three to four months, or who had prior exposure to a monoclonal antibody with CGRP inhibition as a mechanism of action. Patients with major cardiovascular and other major comorbid diseases, including psychiatric disorders that are commonly experienced by patients with migraine, or unfavourable laboratory tests on liver function, for example, were excluded from the studies. In the FOCUS trial, the presence of episodic and chronic migraine during the baseline period was evaluated using triptans or ergot derivatives to treat an established headache, which is not an established ICHD-3 criterion. Finally, the included trials could not assess the comparative longer-term effects of fremanezumab beyond 12 weeks.

Outcomes

Outcomes were defined a priori in CADTH's systematic review protocol. Of these, CDEC discussed the following:

- Change from baseline in MMDs and change from baseline in monthly average number of headache days of at least moderate severity: Data were collected via patient-completed electronic diaries to record the onset and severity of migraine and headache episodes. The MID for reduction in MMDs and in monthly average number of headache days is unclear.
- Change from baseline in monthly use of acute migraine medication: This was defined as intake of medication(s) (per month) to treat headache pain. The MID for reduction in monthly use of acute medication is unclear.
- HIT-6 questionnaire: a scale used to assess migraine-related disability. It measures pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress on a five-point Likert scale. Total scores range from 36 to 78; a higher score indicates a greater impact of the disease on the daily life of the respondent. For patients with episodic migraine, the within-group MID is −2.5 points and the between-group MID is −1.5 points. The between-group MID for patients with chronic migraine has not been established; for chronic daily headaches it is −2.3 points.
- MIDAS questionnaire: a scale used to assess migraine-related disability through five questions regarding the number of days lost and days with significant limitations for work or schoolwork, housework or chores, and family, social, or leisure activities. Two additional questions that are not included in the scoring ask about the frequency of headaches and intensity of headache pain. No MID was identified for this instrument.
- The Work Productivity and Activity Impairment Instrument (WPAI): a self-administered questionnaire that measures impairments in work and activities during the past seven days due to general health or a specific health problem. The questionnaire elicits information on the number of days or hours missed from work, days or hours worked, days during which the performing of work was challenging, and the extent to which the patient was limited at work (work impairment). No migraine-specific MID was found for this instrument.
- Migraine-Specific Quality of Life Questionnaire (MSQoL): MSQoL (version 2.1) questionnaire was used to assess the impact of migraine and migraine treatment on a patient's quality of life during the previous 4 weeks by measuring limitations on normal activities and emotional effects of migraine. Scores range from 0 to 100, with higher scores indicating better health-related quality of life. MIDs are provided for each type section of the questionnaire for patients with 15 or more headache days per month and for patients with chronic migraine.
- EuroQol 5-Dimensions 5-Levels (EQ-5D-5L) questionnaire: included a descriptive system of five dimensions and a visual analogue scalevisual analogue scale assessed at monthly visits. The descriptive system assessed mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Results from the EQ-5D-5L descriptive system can be converted into a single index score ranging from 0 to 1.0, with the possibility of negative scores for societal health states, using a scoring algorithm that takes the local patient and population preferences into account. The non-specific MID estimate = 0.056 for the Canadian population.
- Serious adverse events (SAEs), total adverse events (AEs), withdrawal due to AEs, and notable harms.

The primary outcome in HALO EM and FOCUS was change from baseline in MMDs. The primary outcome in HALO CM was change from baseline in monthly average number of headache days of at least moderate severity.

Efficacy

In HALO CM, the difference in mean change from baseline in the MMDs at 12 weeks was –1.8 days (95% confidence interval [CI], –2.61 to –1.09; P < 0.0001) for the fremanezumab monthly group and –1.7 days (95% CI, –2.48 to -0.97, P <0.0001) for fremanezumab quarterly, compared to placebo. In HALO EM, there was a reduction in MMDs from baseline at 12 weeks of -1.5 days

(95% CI, –2.01 to –0.93; P < 0.0001) for fremanezumab monthly and –1.3 days (95% CI, –1.79 to –0.72, P < 0.0001) for the fremanezumab quarterly treatment groups, versus placebo. In FOCUS, the difference in mean change from baseline in the MMDs at 12-week during the double-blind treatment phase was -3.5 days (95% CI, –4.19 to –2.78, P < 0.0001) between fremanezumab monthly and placebo, and -3.1 days (95% CI, –3.84 to –2.42, P < 0.0001) between fremanezumab quarterly and placebo. The proportion of patients achieving at least 50% reduction in the MMDs during the 12-week double-blind treatment phase of FOCUS was 34% in each of the fremanezumab treatment groups versus 9% in the placebo treatment group. Similar proportions were reported in HALO CM in the fremanezumab treatment groups (31% to 33%); however, there was a larger placebo response (20%).

In HALO CM, the mean reduction of headache days of at least moderate severity at 12 weeks favoured quarterly fremanezumab (–1.8 days; 95% CI, –2.46 to –1.15; P < 0.0001) and monthly fremanezumab (–2.1 days; 95% CI, –2.76 to –1.45; P < 0.0001) compared to placebo. In the FOCUS study, the mean reduction of headache days of at least moderate severity in quarterly fremanezumab compared to placebo was –3.2 days (95% CI, –3.93 to –2.52; P < 0.0001) and –3.6 days (95% CI, –4.30 to –2.91; P < 0.0001) for monthly fremanezumab compared to placebo.

There was an improvement in MIDAS disability scores in HALO EM study, with the mean change from baseline in MIDAS disability scores at 4 weeks after the last dose of study drug of –5.4 points (95% CI, –8.90 to –1.93; P = 0.0023) for quarterly fremanezumab and –7.0 points (95% CI, 10.51 to –3.53; P < 0.0001) for monthly fremanezumab compared to placebo. HIT-6 disability scores improved from baseline in HALO CM at 4 weeks after the last dose of study drug by –1.9 points (95% CI, –2.90 to –0.96; P < 0.0001) for quarterly fremanezumab and –2.4 points (95% CI, –3.32 to –1.38; P < 0.0001) for monthly fremanezumab compared to placebo. In the FOCUS study, exploratory analysis of the mean change from baseline in disability score, as measured by the HIT-6, at 4 weeks after administration of the third dose of study drug showed an improvement in disability score among patients across double-blind treatment groups during the open-label treatment phase.

In the HALO CM study, there was a decrease from baseline in the monthly average number of days of use of any acute headache medication at 12 weeks of –1.8 days (95% CI, –2.43 to -1.12; P < 0.0001) for quarterly fremanezumab and -2.3 days (95% CI, -2.61 to –1.09; P < 0.0001) for monthly fremanezumab compared to placebo. The difference from baseline in the monthly average number of days of use of any acute headache medication at 12 weeks versus placebo was -1.3 days (95% CI, –1.76 to –0.82; P < 0.0001) for quarterly fremanezumab and –1.4 days (95% CI, –1.84 to –0.89; P < 0.0001) for monthly fremanezumab in HALO EM. In FOCUS, the mean change from baseline in the monthly average number of days of use of any acute headache medications during the 12-week double-blind treatment phase compared with placebo were –3.1 days (95% CI, –3.75 to –2.41) and –3.4 days (95% CI, –4.03 to –2.69) for quarterly and monthly fremanezumab, respectively.

Health-related quality of life was measured using several outcome measures, both migraine-specific (e.g., MSQoL) and general (e.g., EQ-5D-5L). While there appeared to be numerical improvements in health-related quality of life with fremanezumab across all three studies, the outcomes were evaluated as exploratory analyses and are considered supportive of a general benefit, but a definitive conclusion regarding fremanezumab's comparative effects on this outcome cannot be made.

Similarly, other patient-valued outcomes such as treatment satisfaction (measured with the Patient Global Impression of Change) and productivity (measured with the Work Productivity and Activity Impairment scale) were evaluated as exploratory outcomes in the trials and were interpreted as supportive evidence.

Harms (Safety)

Most patients treated with fremanezumab (66% to 71%) in HALO CM and HALO EM experienced at least one AE, with the fewest events occurring in the placebo groups (64% and 58% in HALO CM and HALO EM, respectively). Injection site reactions, primarily injection site-related pain, were the most frequently occurring AEs. Most reactions were recorded as mild to moderate in severity and occurred from within hours to one month after administration. One patient in the placebo group of HALO EM experienced a serious injection site reaction. During the double-blind treatment phase of FOCUS, 45% to 55% of patients in the fremanezumab treatment groups, and 48% of patients in the placebo treatment group reported at least one adverse event. As in the other two studies, injection site reactions were the most commonly occurring AEs. Other notable AEs (anti-drug antibody formation, vascular events, constipation, development of hypertension) occurred in 1% or less of patients in all three studies.

SAEs occurred in 3% or less of patients in all three studies. Overall, two patients died, one in the HALO CM 675-mg/placebo/placebo treatment group and the other in the HALO EM fremanezumab 675-mg/placebo/placebo treatment group. The causes of death were assessed by the investigators as unrelated to the study drug. No deaths occurred in the FOCUS study.

Withdrawals due to AEs occurred in 2% or less patients across all three studies.

Indirect Evidence

Two indirect treatment comparisons using network meta-analysis (NMA) were summarized and appraised: one sponsor submitted NMA and one by the Institute of Clinical and Economic Reviews of fremanezumab versus other migraine therapies for adult patients with chronic migraine and episodic migraine. The overall results from both NMAs suggested that fremanezumab has improved clinical efficacy versus placebo in most of the outcomes analyzed. Throughout the various networks in both NMAs, fremanezumab did not show a clearly favourable, or unfavourable, effect versus other prophylaxis medications for migraine.

Only the sponsor submitted NMA included studies that had clearly indicated the proportion of the included patient population with chronic migraine, episodic migraine, and the number of previous inadequate treatments. This variation in the approach to data synthesis meant that the sponsor submitted NMA would include a more homogenous population than the Institute of Clinical and Economic Reviews one, albeit with networks that were more spare and smaller in sample size. The smaller network sizes means there is less precision (wide 95% credible intervals), the consistency assumption could not be tested, and a fixed-effects model instead of random effects was used, which adds another layer of unverifiable assumptions to the model. The sponsor submitted NMA included the FOCUS trial in the networks with two or more inadequate previous treatments without separating the chronic migraine patients from patients with episodic migraine. This approach violated the sponsor submitted NMA eligibility criteria, where many other trials were excluded for not providing data separately for each migraine type, and, more concerning, introduced considerable clinical heterogeneity in the networks. This likely biased the results in favour of fremanezumab in the episodic migraine networks and against fremanezumab in the chronic migraine networks, assuming a potentially larger treatment effect in the chronic migraine population.

Other Relevant Evidence

The HALO long-term study (LTS) (N = 1,890) was a multi-centre, randomized, double-blind, parallel-group, phase III study of subcutaneous administration of fremanezumab for the preventive treatment of migraine in adults. Patients who had completed HALO CM and HALO EM were eligible for HALO LTS, as well as new patients (16.5%) who had not participated in the HALO CM or HALO EM studies. Patients who received placebo during the pivotal studies and newly enrolled patients were randomized 1:1 to either monthly or quarterly fremanezumab treatment. Patients who had received fremanezumab as either monthly or quarterly dosing in the pivotal studies continued with the same dosing regimen for 12 months along with a 6.5-month post-treatment follow-up.

For both migraine classifications and both treatment groups, the mean number of migraine days per month and headache days per month of at least moderate severity decreased from baseline and remained stable for the duration of the study. The use of acute headache medication followed a similar trend during the LTS.

HIT-6 and MIDAS scores, for chronic migraine and episodic migraine patients, respectively, showed a decrease for both dosing groups over time indicating patients continued to experience reduced migraine-related disability past the initial 12 weeks treatment periods of the pivotal HALO studies. Quality of life measures (MSQoL and EQ-5D-5L) and patient-reported assessment of clinical change after treatment (PGIC) showed improvements in most patients during the HALO LTS. PHQ-9 scores (for assessing depression in patients) and WPAI scores (how migraine affects work and daily life) both decreased from baseline to end of treatment suggesting improved patient outcomes during the LTS.

Most patients (85%) experienced an AE, and 10% experienced a SAE. Injection site induration, pain, and erythema were the three most common AEs occurring in 619 (33%), 580 (31%), and 497 (26%) patients, respectively. The two most common SAEs were status migrainosus and basal cell carcinoma, both occurring in 4 patients (< 1%) each. Seventy-six (4%) patients discontinued the study due to AE which occurred at a similar frequency (3% to 5%) across the three groups. One death occurred in the fremanezumab 675 mg quarterly group approximately 300 days after the last dose of the study drug. The patient had a brain aneurysm and multiple strokes.

HALO LTS did not contain a placebo arm or other treatment comparator. Nearly 20% of the overall intention-to-treat population discontinued the study. As part of the eligibility criteria for the LTS, patients had to complete one of the pivotal studies and not all patients who completed the HALO studies rolled over to the LTS. Additionally, patients who discontinued the pivotal studies due to AEs were excluded. Thus, HALO LTS likely represents a highly selective patient population.

Cost and Cost-Effectiveness

Fremanezumab is available as a 150 mg/mL pre-filled syringe, at a submitted price of $585 per syringe. The annual per patient drug acquisition cost of fremanezumab is $7,020.

The sponsor submitted a cost-utility analysis to assess the cost-effectiveness of fremanezumab for the prevention of migraine in adults compared to erenumab, galcanezumab, and placebo (BSC) among patients with episodic migraine (< 15 monthly headache days of which 4 to 15 are MMDs) or chronic migraine (≥ 15 monthly headache days of which ≥ 8 are MMDs), stratified by the number of prior preventive migraine therapies (< 2, ≥ 2). OnaA was also considered as a comparator in analyses involving patients with chronic migraine and greater than or equal to 2 prior preventive migraine treatments. The sponsor's analysis was conducted from the perspective of a Canadian publicly funded health care payer over a 10-year horizon. The pharmacoeconomic submission was based on a Markov model, which comprised three-state health states: on-treatment, off-treatment, or death. Patients entered the model experiencing a baseline number of MMDs, reflective of the baseline migraine frequency in the HALO CM, HALO EM, and FOCUS trials. Treatment effectiveness was defined as a reduction in MMDs relative to placebo, with relative treatment effects obtained from sponsor-provided network meta-analyses. In the sponsor's base case, fremanezumab was associated with an incremental cost effectiveness ratio (ICER) of $138,122 to $348,676 per QALY, depending on subgroup (episodic migraine; chronic migraine; or < 2, ≥ 2 prior preventive migraine therapies). Fremanezumab was extendedly dominated by OnaA and galcanezumab among patients with chronic migraine and greater than or equal to 2 prior preventive migraine therapies.

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

- Galcanezumab and erenumab are not currently reimbursed on public formularies in Canada.
- There is no direct head-to-head evidence comparing fremanezumab with other currently available preventive migraine therapies.
- Treatment effectiveness was based on a reduction in the number of MMD; however, treatment decisions in practice consider migraine severity and/or frequency, which were not reflected within the sponsor's economic analysis.
- Subsequent preventive migraine treatment after fremanezumab discontinuation was not considered.
- The clinical effects of fremanezumab observed in 12-week trials were assumed to be maintained for 10 years.
- Health care resource use was based on US data and may not reflect migraine management in Canada.

CADTH undertook reanalyses to address the identified limitations, including comparing fremanezumab to BSC, reducing the time horizon to 5 years, and removing costs related to hospitalization. CADTH was unable to address the structural limitations related to a lack of consideration of patient-important outcomes of treatment (e.g., severity of migraine headaches). CADTH's reanalyses found the following:

- Episodic migraine:
  - Less than 2 prior preventive migraine therapies: ICER = $377,664; Price reduction (PR) to meet a $50,000 per QALY WTP threshold: 90%
  - Greater than or equal to 2 prior preventive therapies: ICER = $164,243; PR to meet a $50,000 per QALY WTP threshold: 71%
- Chronic migraine:
  - Less than 2 prior preventive therapies: ICER = $257,610; PR to meet a $50,000 per QALY WTP threshold: 83%
  - Greater than or equal to 2 prior preventive therapies: ICER = $128,950; PR to meet a $50,000 per QALY WTP threshold: 61%

Fremanezumab was not cost-effective compared to BSC at a $50,000 per QALY WTP threshold in any subgroup.

CDEC Members

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Regrets

None

Conflicts of Interest

None

CADTH

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