CADTH

CADTH Drug Reimbursement Review

Pharmacoeconomic Report

FREMANEZUMAB (AJOVY)

(Teva Canada Innovation)

Indication: For the prevention of migraine in adults who have at least 4 migraine days monthly

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CADTH

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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

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Abbreviations

BSC	best supportive care
CDEC	CADTH Canadian Drug Expert Committee
CDR	CADTH Common Drug Review
CGRP	calcitonin gene–related peptide
CM	chronic migraine
EM	episodic migraine
EQ-5D	EuroQol 5-Dimensions
ICER	incremental cost-effectiveness ratio
INESSS	Institut national d'excellence en santé et en services sociaux
MMD	monthly migraine day
MSQoL	Migraine-Specific Quality of Life
NMA	network meta-analysis
OnaA	onabotulinumtoxin A
QALY	quality-adjusted life-year
WTP	willingness to pay

Executive Summary

The executive summary comprises 2 tables (Table 1: Background and Table 2: Economic Evaluation) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Fremanezumab (Ajovy), solution for subcutaneous injection
Submitted price	Fremanezumab, 150 mg/mL: $585.00 per single-dose pre-filled syringe
Indication	For the prevention of migraine in adults who have at least 4 migraine days per month
Health Canada approval status	NOC
Health Canada review pathway	Standard
NOC date	April 9, 2020
Reimbursement request	As per indication
Sponsor	Teva Canada Innovation
Submission history	Previously reviewed: No

NOC = Notice of Compliance.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis
Target population	Adults who have at least 4 migraine days per month
Treatment	Fremanezumab, 225 mg subcutaneous injection: 225 mg monthly or 675 mg quarterly
Comparators	Placebo, erenumab, galcanezumab, OnaA (chronic migraine, ≥ 2 prior preventive therapies subgroup only)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	10 years
Key data source	Indirect treatment comparison
Submitted results for base case	**Episodic migraine** • < 2 prior preventive migraine therapies: ICER = $348,676 per QALY (incremental cost $13,888; incremental QALYs: 0.04) compared with placebo • ≥ 2 prior preventive therapies: ICER = $138,122 per QALY (incremental cost $12,198; incremental QALYs: 0.09) compared with placebo **Chronic migraine** • < 2 prior preventive therapies: ICER = $234,051 per QALY (incremental cost $13,446; incremental QALYs: 0.06) compared with placebo • ≥ 2 prior preventive therapies: ICER = $102,184 per QALY (incremental cost $11,649; incremental QALYs: 0.114) compared with placebo
Key limitations	• The sponsor's base case included galcanezumab and erenumab as comparators, which are not currently reimbursed on public formularies in Canada. CADTH compared fremanezumab with placebo (hereafter referred to as best supportive care [BSC]) in the CADTH base case, and with galcanezumab and erenumab in scenario analyses. • There is no direct head-to-head evidence comparing fremanezumab with other currently available preventive migraine therapies. The sponsor conducted a network meta-analysis (NMA) comparing fremanezumab, erenumab, galcanezumab, and OnaA (OnaA was considered only among chronic migraine patients ≥ 2 prior preventive migraine therapies). In the CADTH base case comparing fremanezumab with BSC,

Component	Description
	CADTH used the sponsor's NMA estimates to inform clinical efficacy parameters; the impact of using direct efficacy estimates from the FOCUS, HALO CM, and HALO EM studies was tested in scenario analyses. • Treatment effect was modelled in terms of a reduction in the number of MMD. Instead, as indicated by clinical experts consulted by CADTH, reductions in migraine severity and/or frequency would be more relevant. • The sponsor's pharmacoeconomic model does not adequately reflect the clinical management of migraine. Patients who discontinue treatment are assumed to receive no further preventive migraine therapies. In practice, patients who discontinue fremanezumab would receive an alternative preventive migraine treatment. The sponsor's model does not consider subsequent treatment after fremanezumab discontinuation, limiting its ability to reflect the anticipated use of fremanezumab. • The sponsor assumed that the clinical effects of fremanezumab observed in 12-week trials would be maintained for 10 years. • Health care resource use was based on utilization data from the US and may not reflect the management of migraine in Canada.
CADTH reanalysis results	In the CADTH reanalyses, costs related to hospitalization were removed, the time horizon was reduced to 5 years, and fremanezumab was compared with BSC. Based on CADTH reanalyses, the ICER for fremanezumab is **Episodic migraine** • < 2 prior preventive migraine therapies: ICER = $377,664 per QALY (incremental cost $13,865; incremental QALYs: 0.04) compared with BSC • ≥ 2 prior preventive therapies: ICER = $164,243 per QALY (incremental cost $13,571; incremental QALYs: 0.08) compared with BSC **Chronic migraine** • < 2 prior preventive therapies: ICER = $257,610 per QALY (incremental cost $13,752; incremental QALYs: 0.05) compared with BSC • ≥ 2 prior preventive therapies: ICER = $128,950 per QALY (incremental cost $13,436; incremental QALYs: 0.10) compared with BSC In all subgroups, price reductions would be required in order for fremanezumab to be considered optimal at a WTP threshold of $50,000 per QALY (range: 61% to 90%).

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life-year; NMA = network meta-analysis; OnaA = onabotulinumtoxin A; QALY= quality-adjusted life-year; WTP = willingness to pay.

Conclusions

CADTH undertook reanalyses to address limitations in the sponsor's submission, including adopting best supportive care (BSC) as the comparator, changing the time horizon to 5 years, and removing costs related to hospitalization for the treatment of migraine. In CADTH's reanalyses, fremanezumab was more effective and more costly than BSC in all patient subgroups (episodic migraine [EM], chronic migraine [CM]), regardless of number of prior preventive migraine therapies (< 2, ≥ 2). Price reductions of 61% to 90% would be required for fremanezumab to be considered optimal compared with BSC at a willingness-to-pay (WTP) threshold of $50,000 per QALY. Interpretation of these results should allow for the fact that migraine severity was not considered in the model.

The clinical effectiveness of fremanezumab relative to other currently reimbursed migraine preventive therapies is uncertain, due to a lack of direct comparative evidence and limitations within the sponsor's network meta-analysis (NMA). In scenario analyses using results from the sponsor's NMA, CADTH compared the cost-effectiveness of fremanezumab with erenumab, an anti–calcitonin gene–related peptide (CGRP) drug recently recommended by the CADTH Canadian Drug Expert Committee (CDEC) for the prevention

of CM. Among patients with EM or CM, regardless of previous treatment experience, there were minimal differences in costs and quality-adjusted life-years (QALYs) between fremanezumab and erenumab. The results of these analyses suggest that fremanezumab and erenumab may be equivalent in both costs and effectiveness among all subgroups; however, these results should be interpreted with caution, as they are based on an uncertain NMA and the list price of erenumab (rather than the negotiated reimbursed price).

Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups that participated in the CADTH review process.

CADTH received 1 patient input submission, which was a joint effort between Migraine Canada and Migraine Quebec, for the review of fremanezumab for the treatment of migraine. Patient input was gathered through an online survey with 597 respondents (see the Patient Input section of the CADTH Common Drug Review (CDR) clinical report[1] for more details). Of the respondents, 32% reported 7 to 14 migraines per month, while 42% had at least 15 migraines per month.

In terms of symptoms, patients with migraine report severe, throbbing, recurring pain; nausea; vomiting; dizziness; vertigo; loss of balance; extreme sensitivity to sound, light, touch, and smell; visual disturbances; loss of vision, speech, sensation, or muscle strength; and tingling or numbness in the extremities or face. Migraines can also be associated with slowed thinking, lack of focus, and difficulty reading and speaking, all of which impact an individual's ability to perform work tasks and socialize with others. In total, 80% of respondents also noted that their migraines have led to anxiety or depression. Patients also reported living in fear of the next attack, dreading potential triggers, and having difficulty planning future events, which limits their personal and professional activities. Of respondents, 27% reported having been to the emergency department at least 4 times since the start of their disease, with some also reporting feeling stigmatized and blamed for wasting health care resources and the time of health care providers. Twenty-seven percent of patients reported having to wait more than a year to see a neurologist or headache specialist, and 54% of patients reported being dissatisfied or very dissatisfied with the care they received from their physicians.

When asked about oral preventive treatments, 11% of respondents had not tried any, 22% had tried 1 or 2 preventives, 22% had tried 3 or 4, and 45% had tried at least 5. Adverse reactions are a key consideration when deciding among treatment options. Seven percent of patients reported not having any side effects, 25% stated that what they experienced was tolerable, and 68% had discontinued a medication because of them. The most common side effects from using preventive medications reported were somnolence (76%), dizziness (58%), weight gain (54%), cognitive difficulties (53%), gastrointestinal upset (45%), and mood difficulties (44%). Patients valued a preventive medication that would allow them to be more productive at work and with their family, provide any degree of relief, have fewer side effects, and be affordable.

Several of these aspects were addressed in the sponsor's model:

- The clinical effectiveness of preventive migraine therapies was based on number of monthly migraine days (MMDs), with higher frequency associated with lower health-related quality of life and higher health care costs.
- Loss of productivity was considered in scenario analyses.

Some aspects were not directly addressed in the sponsor's model and could not be addressed by CADTH owing to structural or data limitations. These were

- effects of treatment on migraine severity
- adverse events related to treatment.

Economic Review

The current review is for fremanezumab (Ajovy) for adults who have at least 4 migraine days per month.

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

Fremanezumab is indicated for the prevention of migraine in adults who have at least 4 MMDs,[2] which is consistent with the sponsor's reimbursement request.[3] The sponsor submitted a cost-utility analysis to assess the cost-effectiveness of fremanezumab among patients with EM (< 15 monthly headache days, of which 4 to 15 are MMDs) or CM (≥ 15 monthly headache days, of which 8 or more are MMDs), stratified by the number of prior preventive migraine therapies (< 2, ≥ 2).[3] Patients with CM are assumed to experience 17.3 MMDs, while patients with EM are assumed to experience 9.3 migraine days, based on data from a sponsor-provided NMA.[3,4] The cost-effectiveness of fremanezumab among all patients with migraine is provided, based on a weighted average of subgroup analyses (assumed prevalence of 91% and 9% for EM and CM, respectively, based on the baseline prevalence of EM and CM in the CaMEO study, a web-based study of migraine in the US).[5]

Fremanezumab is administered by subcutaneous injection, either as 225 mg administered monthly or 675 mg administered quarterly, and is supplied as a solution for injection in a single-dose pre-filled syringe (150 mg/mL).[2] The sponsor's submitted price for fremanezumab is $585 (annual cost of treatment $7,020 per patient).

The sponsor's base-case analyses compared fremanezumab with erenumab, galcanezumab, and placebo (BSC, consisting of acute migraine-specific and nonspecific treatments).[3] Erenumab and galcanezumab are approved by Health Canada for the prevention of migraines in adults with at least 4 MMDs;[6,7] neither treatment is currently reimbursed on public formularies. Onabotulinumtoxin A (OnaA) was considered as a comparator in analyses involving patients with CM and 2 or more prior preventive migraine treatments.[3] Three oral preventive migraine therapies (amitriptyline, propranolol, topiramate) were considered as comparators in scenario analyses.

The sponsor adopted a 10-year horizon, with the analysis conducted from the perspective of the publicly funded health care payer. Future costs and benefits were discounted at a rate of 1.5% per year. The model cycle length was 28 days.

Model Structure

The economic analysis was conducted using a 3-state Markov model, with states related to the use of preventive migraine treatments (On-Treatment, Off-Treatment) or death (Appendix 3).[3] Patients receiving active treatment (i.e., other than BSC) entered the model in the On-Treatment state, and a proportion of patients were assumed to discontinue treatment each cycle (i.e., transition to the Off-Treatment state). Patients in the Off-Treatment state received BSC only (i.e., no additional preventive migraine therapy). The discontinuation rates were intended to reflect the patient's decision to discontinue treatment and were obtained from a previous cost-effectiveness analysis of erenumab.[8] The rate of discontinuation for fremanezumab and galcanezumab was assumed to be equal to that for

erenumab (3.71% per cycle) and were applied on a 4-week basis, while discontinuation for OnaA was applied on a 12-week basis (23.98% per cycle).[3]

The primary measure of efficacy in the model was the reduction in the number of MMDs per 28 days relative to placebo. The efficacy estimates were obtained from sponsor-provided NMAs and were modelled as a decrease relative to a "longitudinal placebo CM 12-week MD [migraine day] value derived from a non-linear extrapolation of fremanezumab pivotal clinical trial data."[3]

Model Inputs

Data from the HALO CM,[9] HALO EM,[10] and FOCUS[11] trials were used to inform the demographic characteristics of patients with 2 or more and fewer than 2 prior preventive migraine therapies, respectively. Each was a phase III, multi-centre, randomized controlled trial, but they used different treatment durations and inclusion criteria. HALO CM and HALO EM enrolled participants aged 18 to 70 years with history of CM or EM, respectively, and randomized participants to fremanezumab administered monthly (225 mg), fremanezumab administered quarterly (675 mg), or placebo.[9,10] FOCUS enrolled participants aged 18 to 70 years with either CM or EM who had previous inadequate response to 2 to 4 classes of preventive migraine medications, and similarly randomized participants to monthly (225 mg) or quarterly (675 mg) fremanezumab or placebo.[11]

The primary measure of efficacy in the model was the reduction in the number of MMDs per 28 days relative to placebo. The efficacy estimates were obtained from sponsor-provided NMAs[4] and were modelled as a decrease relative to a "longitudinal placebo CM 12-week MD value derived from a non-linear extrapolation of fremanezumab pivotal clinical trial data."[3] The efficacy of fremanezumab was based on the weighted average of the NMA efficacy estimates for monthly or quarterly dosage based on the number of patients who received each treatment in the clinical trials.[3] Similarly, the efficacy of erenumab (70 mg and 140 mg) was based on a similarly weighted average, while the efficacy of galcanezumab was based on the 120 mg dose.[3]

Mortality was based on Statistics Canada estimates of age- and gender-specific general population mortality rates[12] and was weighted by the proportion of male and female patients in the HALO[9,10] and FOCUS[11] trials. Mortality was assumed to be independent of the number of MMDs and treatment received.

Health state utility values were determined by the number of MMDs experienced by the patient per 28-day cycle. Utility values were derived from the Migraine-Specific Quality of Life (MSQoL) questionnaire estimates from the FOCUS[11] trial, mapped to the EuroQol 5-Dimensions (EQ-5D) questionnaire by use of a mapping approach.[13] Utilities for patients in the On-Treatment health state were based on data from participants who received fremanezumab as part of the FOCUS[11] trial and were assumed to be equivalent across comparators and between the On-Treatment and Off-Treatment health states.

The economic model included drug costs for migraine prevention, as well as "disease management costs."[3] The price of fremanezumab was based on the sponsor's submitted price.[3] The prices of erenumab and galcanezumab were obtained from the Association québécoise des pharmaciens propriétaires (erenumab) and Teva (galcanezumab), while the price of OnaA was obtained from the Ontario Drug Benefit Formulary.[14] Administration costs were incorporated only for OnaA.[15]

Disease management costs included drug costs for acute migraine treatment (migraine-specific and nonspecific treatments) and migraine-related health resource use (i.e., general practitioner visits, emergency department visits, specialist visits, hospitalizations). Migraine-specific acute treatments included triptans and ergot derivatives; nonspecific treatments included acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), barbiturates, opioids, isometheptene compounds, and "other over-the-counter medications."[3] Acute migraine treatment was incorporated in the model as "migraine-specific acute medication days" and "nonmigraine-specific acute medication days," with the number of acute medication days determined by the number of MMDs, adopted from an economic evaluation of erenumab.[8] The cost per day of acute migraine treatment (specific and nonspecific) was obtained from a previous economic evaluation,[8] converted to Canadian dollars,[16] and multiplied by the number of medication days.

Health care resource utilization was based on the number of MMDs and was adopted from an economic evaluation of erenumab[8] and a 2006 US survey of 7,437 migraine patients.[17] Costs for general practitioner and specialist visits were obtained from the Ontario Schedule of Benefits for Physician Services,[15] while the costs for emergency department visits and hospitalizations were obtained from the Ontario Case Costing Initiative.[18]

All costs are presented in 2019 Canadian dollars.[3]

Summary of Sponsor's Economic Evaluation Results

The sponsor submitted probabilistic analyses aligned with the reimbursement request (adults with at least 4 MMDs), for all patients with migraine, as well as for patients with CM or EM, stratified by the number of prior preventive migraine therapies. The sponsor's cost-effectiveness analysis was based on 2,500 probabilistic iterations, for which findings are presented in this section. Additional results from the sponsor's submitted economic evaluation base case are presented in Appendix 3.

Base-Case Results

The sponsor's base-case results for all patients with migraine are presented in Table 3. This estimate was based on a weighted pooling of the total expected costs and QALYs for each subgroup (Table 4) according to an assumed distribution of migraine patients and prior preventive therapies.[3]

Among all patients with migraine, fremanezumab compared with BSC was associated with a QALY gain of 0.09 at an additional cost of $12,371, resulting in an incremental cost-effectiveness ratio (ICER) of $145,986 per QALY gained. Uncertainty estimates are unavailable from this analysis, as this was a weighted sum of subgroup analyses.

Table 3: Summary of the Sponsor's Economic Evaluation Results — Overall Population

Drug	Total costs[a] ($)	Total QALYs[a]	Sequential ICER ($/QALY)
Placebo	45,690	5.899	—
Erenumab	57,943	5.948	Extendedly dominated
Fremanezumab	58,061	5.984	145,986
Galcanezumab	60,170	5.971	Dominated

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

[a] Weighted based on anticipated use (79.3% EM with 2 or more prior preventive migraine therapies, 11.9% EM with less than 2 prior preventive therapies, 7.7% CM with 2 or more prior preventive therapies, 1.1% CM with less than 2 prior preventive therapies).[3]
Source: Sponsor's pharmacoeconomic submission.[3]

Subgroup Analyses

Subgroup analyses by type of migraine (EM, CM) and number of prior preventive migraine therapies (< 2, ≥ 2) are provided in Table 4. The sponsor's analyses included erenumab and galcanezumab as comparators in all subgroups; OnaA was included for CM with 2 or more prior preventive migraine therapies only. Additional details of the sponsor's analyses are shown in Appendix 3.

Among patients with EM and fewer than 2 prior preventive migraine therapies, fremanezumab versus placebo is associated with a QALY gain of 0.04 at an additional cost of $13,888, resulting in an ICER of $348,676 per QALY. At a WTP threshold of $50,000 per QALY, there is a 0.5% probability of fremanezumab being optimal.

Among patients with EM and 2 or more prior preventive migraine therapies, fremanezumab versus placebo is associated with a QALY gain of 0.09 at an additional cost of $12,198, resulting in an ICER of $138,122 per QALY gained. At a WTP threshold of $50,000 per QALY, there is a 6% probability of fremanezumab being optimal.

Among patients with CM and fewer than 2 prior preventive migraine therapies, fremanezumab versus placebo is associated with a QALY gain of 0.06 at an additional cost of $13,446, resulting in an ICER of $234,051 per QALY gained. At a WTP threshold of $50,000 per QALY, there is a 1% probability of fremanezumab being optimal.

Among patients with CM and 2 or more prior preventive migraine therapies, fremanezumab was extendedly dominated by OnaA and galcanezumab. At a WTP threshold of $50,000 per QALY, there is a 2% probability of fremanezumab being optimal.

Table 4: Summary of the Sponsor's Economic Evaluation Results — Subgroup Analyses

Drug	Total costs ($)	Total QALYs	Sequential ICER ($/QALY)
Episodic migraine, < 2 prior preventive therapies			
Placebo	42,442	6.022	—
Erenumab	55,153	6.057	Extendedly dominated
Fremanezumab	56,330	6.062	348,676
Galcanezumab	57,949	6.063	1,551,908
Episodic migraine, ≥ 2 prior preventive therapies			
Placebo	42,319	6.004	—
Fremanezumab	54,517	6.093	138,122
Erenumab	54,684	6.049	Dominated
Galcanezumab	56,815	6.075	Dominated
Chronic migraine, < 2 prior preventive therapies			
Placebo	80,712	4.805	—
Erenumab	93,310	4.847	Extendedly dominated
Fremanezumab	94,158	4.862	234,051
Galcanezumab	97,072	4.822	Dominated
Chronic migraine, ≥ 2 prior preventive therapies			
Placebo	80,424	4.788	—
Onabotulinumtoxin A	82,568	4.829	51,684
Erenumab	90,749	4.901	Extendedly dominated

Drug	Total costs ($)	Total QALYs	Sequential ICER ($/QALY)
Fremanezumab	92,073	4.902	Extendedly dominated
Galcanezumab	92,869	4.928	104,057

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Note: The submitted analysis is based on the publicly available prices of the comparator treatments and does not reflect negotiated price reductions.

Source: Sponsor's pharmacoeconomic submission.[3]

Sensitivity and Scenario Analysis Results

The sponsor provided several scenario and sensitivity analyses. These included varying the time horizon; varying the discount rate for costs and outcomes; taking a societal perspective (i.e., including productivity costs); excluding treatment discontinuation; incorporating treatment-specific utilities; adopting stopping rules; and incorporating alternative comparators (i.e., oral treatments [amitriptyline, propranolol, topiramate], OnaA in patients with CM and fewer than 2 prior therapies). These scenario analyses did not include placebo/BSC as a comparator.

In the scenario analysis that compared fremanezumab with oral prophylactic treatments, fremanezumab was not cost-effective in any subgroup compared with oral treatments at a WTP threshold of $50,000 per QALY (Table 15). The cost-effectiveness of fremanezumab was most sensitive to changes in treatment stopping rules and response rate among patients with EM. Among patients with CM, cost-effectiveness was most sensitive to changes in the analysis perspective and the response rate.

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the economic analysis:

- **The anti-CGRP comparators (galcanezumab, erenumab) included in the sponsor's model are not currently reimbursed on public formularies in Canada.** Galcanezumab and erenumab both have received Health Canada approval for migraine prophylaxis[6,7] but are not currently reimbursed on public formularies. Erenumab was recently reviewed by CDEC,[19] while galcanezumab has not been submitted for consideration.

CADTH compared fremanezumab with BSC in the base case, and with galcanezumab and erenumab in scenario analyses. BSC was assumed to consist of migraine-specific acute medication (triptans, ergot derivatives) and nonmigraine-specific acute medication (acetaminophen, NSAIDs, barbiturates, opioids, isometheptene compounds, other over-the-counter medications), as described in the sponsor's submission.[3]

- **The comparative clinical effectiveness of fremanezumab relative to other preventive migraine treatments is uncertain.** There was no direct head-to-head evidence for fremanezumab versus other anti-CGRPs, OnaA, or oral preventive migraine treatments. The sponsor used the results from its NMA to estimate the number of MMDs avoided with fremanezumab compared with placebo, erenumab, galcanezumab, and OnaA; oral preventive treatments were not included in the NMAs. As noted in the CADTH clinical review,[1] the interpretation of the sponsor's NMA findings is limited by heterogeneity among the included patients, which may bias the results in favour of fremanezumab in the EM network and against fremanezumab in the CM network. The incremental QALYs predicted by the model based on the NMA results should therefore be interpreted with a higher degree of uncertainty than is reflected in the probabilistic analysis when comparing these treatments in all subgroups. Consequently, the NMA is not sufficient to conclude whether fremanezumab is superior, inferior, or equivalently effective to other comparators.

There are many additional prophylactic treatments available for the treatment of migraine (Table 11 and Table 12). Canadian guidelines include first-line (propranolol, metoprolol, nadolol, amitriptyline, nortriptyline), second-line (topiramate, candesartan, gabapentin), and "other" treatments (divalproex, pizotifen, OnaA, flunarizine, venlafaxine).[20] Based on the feedback from clinical experts consulted by CADTH for the review, propranolol, amitriptyline, and topiramate are commonly used for migraine prophylaxis in Canada.

- The CADTH base case compared fremanezumab with BSC, with efficacy estimates based on the sponsor's NMA. The cost-effectiveness of fremanezumab compared with erenumab, galcanezumab, OnaA, and oral preventive migraine treatments (i.e., topiramate, amitriptyline, propranolol) was explored in scenario analyses. The cost-effectiveness of fremanezumab relative to other treatments indicated for migraine prophylaxis (Table 8) is unknown.
  - **The model structure does not adequately reflect the management of migraine in clinical practice.** The health states used by the sponsor to assess the cost-effectiveness of fremanezumab classify patients as On-Treatment or Off-Treatment, with effectiveness defined as reduction in mean migraine days per 28 days. Patients who are Off-Treatment (e.g., discontinue fremanezumab) were assumed to receive BSC (acute migraine treatment) only, with no additional preventive therapy. According to clinical experts consulted by CADTH, patients who discontinue fremanezumab would continue to receive preventive migraine treatment, which may consist of another anti-CGRP, OnaA (depending on prior treatment experience), or an oral preventive treatment (e.g., propranolol, amitriptyline, topiramate). The sponsor's assumption that patients would receive no additional preventive treatment was not based on data.[3] This assumption is also in contrast with the opinion of clinical experts contacted by the sponsor ("Canadian clinical experts contacted by Teva have indicated that patients are unlikely to return to placebo"[3]).

Clinical effects in the sponsor's model were based on the number of migraine days experienced by the patients and does not capture other clinically meaningful aspects of the condition, such as headache severity. According to clinical experts consulted by CADTH, patients may find a reduction in the severity of their migraine headaches, without a reduction in the frequency of headaches, to be a clinically meaningful outcome. Additionally, a reduction in the frequency of migraines may not necessarily be associated with a reduction in severity.

- CADTH was unable to address these limitations associated with the model structure. The direction and magnitude of the impact on the cost-effectiveness results for fremanezumab are unknown.
  - **Uncertainty in the long-term treatment efficacy of fremanezumab.** In the sponsor's model, patients On-Treatment were assumed to maintain improved frequency of MMDs achieved in the first 24 weeks for the remainder of the analysis time horizon. This assumption was not explicitly made or justified. FOCUS, HALO CM, and HALO EM studies assessed a 12-week treatment period, and patients who receive a quarterly injection would have received only 1 dose of fremanezumab during this period. As noted in the CADTH clinical review,[1] in a long-term extension of the HALO study, the mean number of MMDs decreased from baseline to month 12.The clinical experts consulted by CADTH indicated that patients may continue to receive benefit for the duration of anti-CGRP treatment; however, an estimated 20% of patients may stop benefiting from prophylactic treatment.[21] The assumption that treatment effects will be maintained for the entire model time horizon favours fremanezumab. However, only up to 2.5% of the QALY benefit observed in the sponsor's base case with fremanezumab, compared with BSC, was from the observed period for which there were trial data.
- CADTH explored the impact of treatment waning in scenario analyses. CADTH also considered a shorter time horizon (5 years rather than the sponsor's submitted 10 years) in the base case.

- **Uncertainty in the frequency estimates for direct health care resource use.** The sponsor stated that resource use estimates were adopted from published sources.[8,17] In the economic evaluation by Lipton et al. (2018),[8] the average annual medical resource use was taken from a 2006 survey of 7,437 migraine patients in the US. Lipton et al. estimated the "use per migraine day" by dividing the mean patient-reported medical resource use over 12 months by the reported annual number of headache days (19 headache days over the previous 12 months). In its model, the sponsor multiplied the "use per migraine day" by the number of migraine days per 28-day cycle to estimate the resource use per cycle, which was assumed to be equivalent between CM and EM patients. The 2006 survey[17] had a 54% response rate and was based on a 12-month recall period. The relationship between data sources and the calculation of resource use per migraine day was not transparently described.

- The clinical expert consulted by CADTH indicated that the management of migraine differs between Canada and the US. Of relevance to this review, patients in Canada are rarely admitted to hospital for the treatment of migraine. In the CADTH base case reanalysis, costs related to the hospitalization of patients for treatment of migraine were removed. The impact of this assumption was explored in scenario analyses.

Additional limitations were identified but were not considered to be key limitations.

- **The utility values associated with the number of migraine days are uncertain.** In the sponsor's submission, utility values were based on the number of migraine days per 28-day period.[3] The utilities were estimated based on MSQoL data from the FOCUS study,[11] mapped to the EQ-5D.[13] MSQoL is a 14-item migraine-specific quality-of-life instrument that measures function across 3 domains (role function–restrictive, role function–preventive, emotional state).[22] The mapping approach was not described well or transparently in the sponsor's submission. The mapping algorithm used a UK value set;[13] therefore, the utility values used in the model do not reflect Canadian preferences. Although EQ-5D data were collected in the FOCUS study,[11] the sponsor justified using mapped utilities rather than EQ-5D values as follows: "The decision to use MSQoL data rather than EQ-5D-3L [3-Levels] data collected during the FOCUS study was made in consideration of the fact that the EQ-5D data were collected at a clinic visit when the patient is less likely to be experiencing a migraine day. As a result, it was determined that the EQ-5D data did not appropriately reflect the utilities associated with monthly migraine days." The location of collection of MSQoL data was not described either in the pharmacoeconomic report[3] or the clinical study report.[11]
  - The use of mapping algorithms is common in economic evaluations. Given that utilities are specified based on health state and are not treatment-specific, the use of a different mapping algorithm is expected to affect only the amount of uncertainty around the mean estimate of the ICER. Given that the CADTH base case had a 0% probability of cost-effectiveness for fremanezumab versus BSC, scenario analysis did not contribute additional information and is not presented.
- **The natural history of migraine disease course has not been incorporated in the model**. The model does not consider changes in the frequency of migraine that are unrelated to treatment (i.e., no patients naturally improve or decline). According to the clinical expert consulted by CADTH, some patients may show a natural improvement or worsening in the frequency of migraines over time, regardless of treatment, transitioning between EM and CM.
  - The effect of this assumption on the model results is unknown but is not expected to meaningfully affect the ICER, as this phenomenon would be biased neither for nor against any particular treatment.

Additionally, the following key assumptions were made by the sponsor and have been appraised by CADTH (Table 5).

Table 5: Key Assumptions of the Submitted Economic Evaluation (Not Noted As Limitations to the Submission)

Sponsor's key assumption	CADTH comment
Starting age of the patient cohorts were based on the FOCUS trial (≥ 2 prior preventive migraine treatments), HALO CM[9] (CM patients, < 2 prior treatments), and HALO EM[10] (EM, < 2 prior treatments).	Uncertain. The mean age of patients in the FOCUS[11] trial, which included both CM and EM patients, was 46 years. The mean age in HALO CM,[9] and HALO EM[10] was 41 and 42 years, respectively. According to CADTH clinical expert consultation, the average age of patients of patients with migraine may differ by type (EM or CM) and by practice location. Patients with CM may be older than those with EM, in that it takes time for CM to develop, and patients seen in primary care may be a younger than those seen in neurology or specialty clinics.
No migraine-related mortality was assumed.	Appropriate. According to CADTH clinical expert consultation, migraine patients are not at higher risk of death than the general population, although they may be at higher risk of stroke.
In the sponsor's model, the efficacy estimates for fremanezumab were based on combined data for monthly (225 mg) and quarterly (675 mg) administration. Similarly, the estimates for erenumab were based on combined data for the 70 mg and 140 mg doses.	Uncertain. Efficacy values for fremanezumab in the sponsor's model were based on weighted averages of the monthly (225 mg) and quarterly (675 mg) dosing. For erenumab, weighted averages of 70 mg and 140 mg doses were used. For both fremanezumab and erenumab, the estimates were weighted based on number of patients who received each treatment in clinical studies, although it was not stated which studies were considered. As described in the CADTH clinical review,[1] fremanezumab reduced the number of MMDs compared with placebo, with no statistically significant difference between monthly and quarterly administration among patients with EM or CM in the FOCUS,[11] HALO CM,[9] and HALO EM[10] studies. A previous CADTH review of erenumab noted that there was "no substantial difference in the mean reduction of MMDs between erenumab 70 and 140 mg, as shown by the included studies." However, in a recent ICER review of anti-CGRPs,[23] monthly administration of fremanezumab was associated with a greater reduction of MMDs (versus placebo) compared with quarterly administration among CM patients, with no difference between erenumab 70 mg and 140 mg. Among patients with EM, the reduction in MMDs differed between monthly and quarterly dosage of fremanezumab and between erenumab 70 mg and 140 mg. However, the ICER NMAs were not stratified based on the number of previous preventive migraine medications, which may introduce heterogeneity.
Discontinuation rates were obtained from a cost-effectiveness analysis of erenumab.[8] The sponsor assumed that the discontinuation rate for erenumab would be applicable to fremanezumab and galcanezumab.	Uncertain. The description of discontinuation is not transparent. Discontinuation is described as being based on the "patient's decision."[3] In 1 section of the report, this is described as "not due to lack of efficacy or stopping rules" (p. 49); in another section, discontinuation is described as "not due to lack of efficacy or adverse events" (p. 7).[3] In the erenumab economic evaluation cited by the sponsor as the source of the discontinuation rate, discontinuation was "all-cause."[8] The assumption of equivalent discontinuation across anti-CGRPs was not justified by the sponsor.
Adverse events were not considered in the sponsor's pharmacoeconomic submission.	Uncertain. Adverse events were not considered in the sponsor's model (no justification provided). As noted in the CADTH clinical review,[1] serious adverse events were infrequent in the FOCUS,[11] HALO CM,[9] and HALO EM[10] studies. Adverse events were noted to be important in the patient input received for this review. Costs related to adverse events could have been included for completeness; however, this is unlikely to influence model results.

Sponsor's key assumption	CADTH comment
Acute medication costs were based on a previous economic evaluation of erenumab and converted to Canadian dollars.	Uncertain. Acute migraine treatments were incorporated as the number of "migraine-specific acute medication days" and "nonmigraine-specific acute medication days" per 28-day cycle, with the number of days determined by the number of MMD. Both the estimated number of acute medication days and the cost per day was adopted from an economic evaluation of erenumab,[8] converted to Canadian dollars.[16] Acute medications in the model consisted of both prescription and over-the-counter medications. The acute medication costs do not reflect the reimbursed prices from Canadian public formularies and include patient out-of-pocket costs. The cost per acute medication ranged from $1.37 to $6.83 per day, depending on whether the medications were "migraine-specific" or "nonspecific" and the type of migraine (EM, CM). The number of acute medication days ranged from 1.5 to 17.5 per 28-day cycle, depending on type of migraine (EM, CM), reflecting a yearly cost of $32 to $1,552 per patient.
No administration costs were applied for fremanezumab, galcanezumab, and erenumab.	Appropriate. Anti-CGRPs are assumed to be self-administered by the patient and would not incur additional health care costs.
An administration fee was applied for OnaA, based on the Ontario Schedule of Benefits for Physician Services.	Inappropriate. Administration of OnaA is not reimbursed in all provinces, and CADTH clinical expert consultation indicated that the cost of administration is often paid out-of-pocket by patients. CADTH removed the administration fee for OnaA from all relevant analyses.

CGRP = calcitonin gene–related peptide; CM = chronic migraine; EM = episodic migraine; ICER = incremental cost-effectiveness ratio; MMD = monthly migraine day; NMA = network meta-analysis; OnaA = onabotulinumtoxin A.

CADTH Reanalyses of the Economic Evaluation

Base-Case Results

CADTH reanalyses addressed a key limitation of the submitted economic model (Table 6). CADTH was unable to address the structural limitation of the model as it relates to lack of consideration of patient-important outcomes of treatment (e.g., severity of migraine headaches).

Table 6: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
None	—	—
Changes to derive the CADTH base case		
1. Health care resource utilization	Patients with migraine were assumed to be admitted to hospital at a rate dependent on the number of MMDs experienced per 28 days.	Patients with migraine in Canada are rarely admitted to hospital for migraine. Costs related to hospitalization were removed (i.e., the frequency of visits and unit costs were changed to zero).
2. Analysis time horizon	10 years	5 years. Recent CADTH analyses of migraine treatments used time horizons of 3 and 5 years as their base case. The time horizon in this analysis was adjusted to align with these reviews.
3. Comparators	Fremanezumab was compared with placebo, erenumab, and galcanezumab (OnaA was included for CM ≥ 2 prior preventive migraine therapies only)	Fremanezumab was compared with BSC, which was assumed to be equivalent to placebo in the sponsor's submission. BSC was assumed to consist of migraine-specific acute medication (triptans, ergot derivatives) and nonmigraine-specific acute medication (acetaminophen,

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
		NSAIDs, barbiturates, opioids, isometheptene compounds, other over-the-counter medications), as described in the sponsor's submission.[3]
CADTH base case (reanalysis 1 + 2 + 3)	—	Reanalysis 1 + 2 + 3

BSC = best supportive care; MMD = monthly migraine day; NSAID = nonsteroidal anti-inflammatory drug; OnaA = onabotulinumtoxin A.

CADTH's base-case results are presented in Table 7. Additional reanalyses and the disaggregated results are presented in Appendix 4.

Among patients with EM and fewer than prior preventive migraine therapies, fremanezumab was associated with higher costs compared with BSC (incremental: $13,865) and higher QALYs (incremental: 0.037) over a 5-year horizon (ICER = $377,664 per QALY).

Among patients with EM and 2 or more prior preventive migraine therapies, fremanezumab was associated with higher costs compared with BSC (incremental: $13,571) and higher QALYs (incremental: 0.083) over a 5-year horizon (ICER = $164,243 per QALY).

Among patients with CM and fewer than 2 prior preventive migraine therapies, fremanezumab was associated with higher costs compared with BSC (incremental: $13,752) and higher QALYs (incremental: 0.053) over a 5-year horizon (ICER = $257,610 per QALY).

Among patients with CM and 2 or more prior preventive migraine therapies, fremanezumab was associated with higher costs compared with BSC (incremental: $13,436) and higher QALYs (incremental: 0.104) over a 5-year horizon (ICER = $128,950 per QALY).

For all 4 subgroups, there is a 0% probability that fremanezumab is optimal compared with BSC at a WTP threshold of $50,000 per QALY.

Table 7: Summary of the CADTH Reanalysis Results

Drug	Total costs ($)	Total QALYs	ICER ($/QALY)
Episodic migraine, < 2 prior preventive therapies			
BSC	4,397	3.127	—
Fremanezumab	18,263	3.163	377,664
Episodic migraine, ≥ 2 prior preventive therapies			
BSC	4,396	3.118	—
Fremanezumab	17,967	3.201	164,243
Chronic migraine, < 2 prior preventive therapies			
BSC	8,301	2.503	—
Fremanezumab	22,053	2.556	257,610
Chronic migraine, ≥ 2 prior preventive therapies			
BSC	8,247	2.492	—
Fremanezumab	21,683	2.596	128,950

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Scenario Analysis Results

Scenario analyses were conducted using the CADTH base case to investigate the impact of including costs related to hospitalization for the treatment of migraine, alternative estimates of treatment effectiveness (based on direct trial evidence), waning of treatment effectiveness over time, an extended analysis horizon (20 years), discontinuation of patients who achieved less than a 50% reduction in MMDs, alternative comparators (erenumab, galcanezumab, OnaA, topiramate, amitriptyline, propranolol), and adopting a societal perspective (Table 24). Results of these scenario analysis are presented in Appendix 4.

Across all patient subgroups, the inclusion of costs related to hospitalization, time horizon, and perspective had minimal effects on the ICER. Cost-effectiveness was also similar in all subgroups when the direct trial evidence of reduction in MMD was considered instead of the sponsor's NMA.

When the effectiveness of fremanezumab was assumed to wane over time, the ICER for fremanezumab compared with BSC was considerably higher than the base case across all subgroups. Reviewers note that there is no evidence to support this treatment waning scenario, and it was implemented to explore the uncertainty in the long-term efficacy of fremanezumab.

Costs and QALYs were minimally different between fremanezumab and erenumab across all subgroups in scenario analysis. Notably, in the scenario involving oral preventive migraine therapies, fremanezumab was not cost-effective at a $50,000 WTP threshold in any subgroup.

Price-reduction analyses were conducted, in each subgroup, for fremanezumab versus BSC (Table 29 to Table 32). Among patients with EM and fewer than 2 prior preventive therapies, a 90% price reduction would be required for fremanezumab to be considered optimal if a decision-maker's WTP is $50,000 per QALY; a 71% reduction would be required among patients with EM and 2 or more prior treatments. Among patients with CM and fewer than 2 prior preventive therapies, an 83% price reduction would be required for fremanezumab to be considered optimal if a decision-maker's WTP is $50,000; a 61% reduction would be required among patients with CM and 2 or more prior treatments.

Issues for Consideration

- **Availability of anti-CGRP comparators.** Two additional anti-CGRPs have been approved by Health Canada (erenumab, galcanezumab) for the prevention of migraines in adults with at least 4 MMDs,[6,7] although neither is currently reimbursed on public formularies. Erenumab was recently reviewed by CDEC, which recommended that erenumab be reimbursed for the prevention of CM in adults who have had an inadequate response, intolerance, or contraindication to 2 or 3 oral prophylactic migraine medications, with a condition of a price reduction.[19] An additional anti-CGRP, eptinezumab, is currently under review by Health Canada.[24]
- **OnaA is reimbursed for the prevention of migraine in selected jurisdictions.** CDEC recently recommended that OnaA be reimbursed for the prophylaxis of headaches in adults with CM who have had an inadequate response, intolerance, or contraindication to at least 3 oral prophylactic migraine medications.[25] Jurisdictions reimbursing OnaA may wish to consider the impact that approving fremanezumab may have for different approaches to treatment sequencing. The submitted evidence did not allow CADTH to explore treatment sequencing in the cost-effectiveness analysis. Jurisdictions may also wish to consider the impact that administration costs (removed from CADTH's analysis)

may have on patients, who may have to pay for them out-of-pocket. In such cases, treatment with an agent like fremanezumab may become more attractive.

- **Comparison with the erenumab pharmacoeconomic review.** CADTH has previously reviewed erenumab for migraine prophylaxis. In the current review, CADTH implemented several changes to the sponsor's submission to increase consistency between the 2 reviews (e.g., adopting a similar time horizon); however, owing to differences in model structure, clinical effectiveness parameters, health state utility values, and cost inputs, the cost-effectiveness results of these 2 evaluations may not be directly comparable.

Overall Conclusions

Based on the CADTH clinical review, fremanezumab may reduce the frequency of migraine among patients with EM or CM, compared with BSC alone. This interpretation is limited by the fact that the sponsor's submitted pharmacoeconomic model was based solely on the frequency of migraine, without considering severity (which was considered relevant to both patients and clinicians).

CADTH undertook reanalyses to address limitations in the sponsor's submission, including adopting BSC as the comparator, removing costs related to hospitalization for the treatment of migraine, and reducing the time horizon to 5 years. In CADTH's base-case reanalysis, fremanezumab was more costly and more effective than BSC in patients with EM or CM, regardless of the number of prior preventive migraine therapies. For patients with EM, the ICER for fremanezumab compared with BSC is $377,664 per QALY among those with less than 2 prior preventive migraine therapies and $164,243 per QALY among those with 2 or more prior preventive migraine therapies. For patients with CM, the ICER for fremanezumab compared with BSC is $257,610 per QALY among those with 2 or more prior preventive migraine therapies and $128,950 per QALY among those with 2 or more prior preventive migraine therapies. Price reduction was indicated in all subgroups for fremanezumab in order for the drug to be considered optimal at a WTP threshold of $50,000 per QALY. Specifically, among patients with EM, price reductions of 90% and 71% would be required for fremanezumab to be considered optimal among patients with fewer than 2 or 2 or more prior preventive migraine therapies, respectively. Among patients with CM, price reductions of 83% and 61% would be required for fremanezumab to be considered optimal among patients with fewer than 2 or 2 or more prior preventive migraine therapies, respectively.

The clinical effectiveness of fremanezumab relative to other currently reimbursed migraine preventive therapies is uncertain, owing to a lack of direct comparative evidence and limitations of the sponsor's NMA. CADTH scenario analyses using the results of the sponsor's NMA found that fremanezumab was consistently associated with higher QALYs and higher costs compared with oral preventive migraine therapies, in all subgroups. Scenario analysis based on the sponsor's NMA also found that fremanezumab yielded similar incremental costs and QALYs when compared with erenumab. While the results of the model suggest that fremanezumab and erenumab were similarly cost-effective, the NMA was not sufficient to conclude that these 2 treatments are equivalent. CADTH's cost-effectiveness analysis was conducted using the sponsor-submitted list price for all comparators. Given that erenumab was recommended by CDEC with a condition of a reduction in price, fremanezumab should be priced no higher than the negotiated price of erenumab. The uncertainty in the NMA comparing these treatments suggests that further price reduction may be warranted.

Appendix 1: Cost Comparison Table

The comparators presented in Table 8 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs but may include devices or procedures. Costs are manufacturer's list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and, as a result, the table may not represent the actual costs to public drug plans.

Table 8: CDR Cost Comparison Table for Prophylaxis of Migraine

Drug/ comparator	Strength	Dosage form	Price ($)	Recommended dosage	Average daily drug cost ($)	Average annual drug cost ($)
Fremanezumab (Ajovy)	225 mg/1.5 mL	Pre-filled syringe	585.0000[a]	225 mg once a month or 675 mg every 3 months	19.22	7,020
Comparators indicated for prophylaxis of migraine						
Erenumab (Aimovig)	70 mg/mL 140 mg/mL	Autoinjector	532.0000[b]	70 mg or 140 mg subcutaneously monthly	17.48	6,384
Flunarizine (generics)	5 mg	Capsule	0.7348	10 mg daily	1.47	537
Galcanezumab (Emgality)	120 mg/mL	Pre-filled syringe	623.0000[c]	240 mg initial loading dose, then 120 mg once monthly	Maintenance: 20.47	First year: 8,099 Subsequent years: 7,476
Onabotulinumtoxin A (Botox)[d]	50 units 100 units 200 units	Injection vial	178.5000 357.0000 714.0000	155 units to 195 units every 12 weeks	8.50	3,105
Pizotyline/Pizotifen (Sandomigran)	0.5 mg 1 mg	Tablet	0.3972 0.8381	1.0 mg to 6 mg daily	0.79 to 4.77	290 to 1,741
Topiramate (generics)	25 mg 100 mg 200 mg	Tablet	0.2433 0.4583 0.6748	100 mg daily[e]	0.46	167

Notes: All prices are from the Ontario Drug Benefit Formulary (accessed October 2020)[14] unless otherwise indicated and do not include dispensing fees. All recommended dosages from respective product monographs. An average year is assumed to be comprised of 365.25 days. Excess medication in vials is assumed wasted where applicable.

[a] Sponsor's submitted price.

[b] CADTH CDR Pharmacoeconomic report for erenumab, sponsor's submitted price.[21]

[c] IQVIA Delta PA wholesale price, accessed October 2020.

[d] Indicated for use in CM only, 15 or more days per month with headaches lasting 4 hours a day or longer.[26] At the time of this review, onabotulinumtoxin A is only reimbursed for the prevention of migraines in selected jurisdictions (e.g., Alberta).

[e] Daily and annual drug costs assume post-titration maintenance dose.[27]

Table 9: CADTH Cost Comparison Table for Prophylaxis of Migraine (Off-Label Medications)

Drug/comparator	Strength	Dosage form	Price ($)	Recommended dosage	Average daily drug cost ($)	Average annual drug cost ($)
Antiepileptics						
Divalproex sodium[a,b] (generics)	125 mg 250 mg 500 mg	Enteric-coated tablet	0.0724 0.1301 0.2604	500 mg to 1,500 mg per day[a,b]	0.26 to 0.78	95 to 285
Valproic acid[a,b] (generics)	250 mg	Capsule	0.2905	500 mg to 1,500 mg per day[a,b]	0.58 to 1.74	212 to 637
	50 mg/mL	Oral solution	0.0398		0.40 to 1.19	145 to 436
	500 mg	Enteric-coated capsule	0.6356		0.64 to 1.91	232 to 696
Gabapentin[a] (generics)	100 mg 300 mg 400 mg	Capsule	0.0416 0.1012 0.1206	1,200 mg to 1,800 mg per day in 3 doses[a]	0.36 to 0.61	132 to 222
Antidepressants						
Amitriptyline[a,b] (generics)	10 mg 25 mg 50 mg	Tablet	0.0435 0.0829 0.1540	20 mg to 150 mg per day[a,b]	0.09 to 0.46	32 to 169
Doxepin[b] (generic)	10 mg 25 mg 50 mg 75 mg 100 mg	Capsule	0.3423 0.4201 0.7793 1.1131[c] 1.4640[c]	25 mg to 100 mg per day[b]	0.42 to 1.46	153 to 534
Nortriptyline[a,b] (generic)	10 mg 25 mg	Capsule	0.2570 0.5193	20 mg to 150 mg per day[a,b]	0.51 to 3.12	188 to 1,138
Venlafaxine[a,b] (generics)	37.5 mg 75 mg 150 mg	Extended-release capsule	0.0913 0.1825 0.1927	150 mg per day[a,b]	0.19	70
Antihypertensives						
Atenolol[b] (generics)	50 mg 100 mg	Tablet	0.1107 0.1821	100 mg to 150 mg per day[b]	0.18 to 0.0.29	67 to 107
Metoprolol[a,b] (generics)	50 mg 100 mg	Tablet	0.0624 0.1361	100 mg to 200 mg per day[a,b]	0.12 to 0.25	46 to 91
	100 mg 200 mg	Sustained-release tablet	0.1415 0.2568		0.14 to 0.26	52 to 94
Nadolol[a,b] (generics)	40 mg 80 mg 160 mg	Tablet	0.4512 0.3710 1.2046	80 mg to 160 mg per day[a,b]	0.37 to 0.74	136 to 271
Propranolol[a,b] (generics)	10 mg 20 mg 40 mg 80 mg	Tablet	0.0689 0.1107 0.1225 0.2034	80 mg to 160 mg per day in 2 doses[a,b]	0.24 to 0.41	89 to 149
Verapamil[a,b] (generics)	80 mg 120 mg	Tablet	0.2735 0.4250	240 mg to 320 mg per day[a,b]	0.82 to 1.12	300 to 410

Drug/comparator	Strength	Dosage form	Price ($)	Recommended dosage	Average daily drug cost ($)	Average annual drug cost ($)
	120 mg 180 mg 240 mg	Sustained-release tablet	0.5078[c] 0.5204 0.5075		0.51[d]	185
Candesartan[a] (generics)	4 mg 8 mg 16 mg 32 mg	Tablet	0.1700 0.2281 0.2281 0.2281	16 mg per day[a]	0.23	83
Lisinopril[a] (generics)	5 mg 10 mg 20 mg	Tablet	0.1347 0.1619 0.1945	20 mg per day[a]	0.19	71
Antimanic/mood stabilizer						
Lithium carbonate[b] (generics)	150 mg 300 mg 600 mg	Capsule	0.0667 0.0657 0.1988[d]	300 mg 3 times daily[b]	0.20	72
Lithium carbonate[b] (Lithmax)	300 mg	Sustained-release tablet	0.2660[d]		0.80	291

All prices are from the Ontario Drug Benefit Formulary (accessed October 2020)[14] unless otherwise indicated and do not include dispensing fees. An average year is assumed to be comprised of 365.25 days.

[a] Source: 2012 Canadian Headache Society Guideline for Migraine Prophylaxis.[28]

[b] Source: Canadian Pharmacists Association, Therapeutic Choices: Medications for Migraine Prophylaxis (accessed October 2020).[29]

[c] Saskatchewan Formulary list price (accessed October 2020).[30]

[d] Assumes 240 mg, as 320 mg is not a possible dose with sustained-release tablets.

Appendix 2: Submission Quality

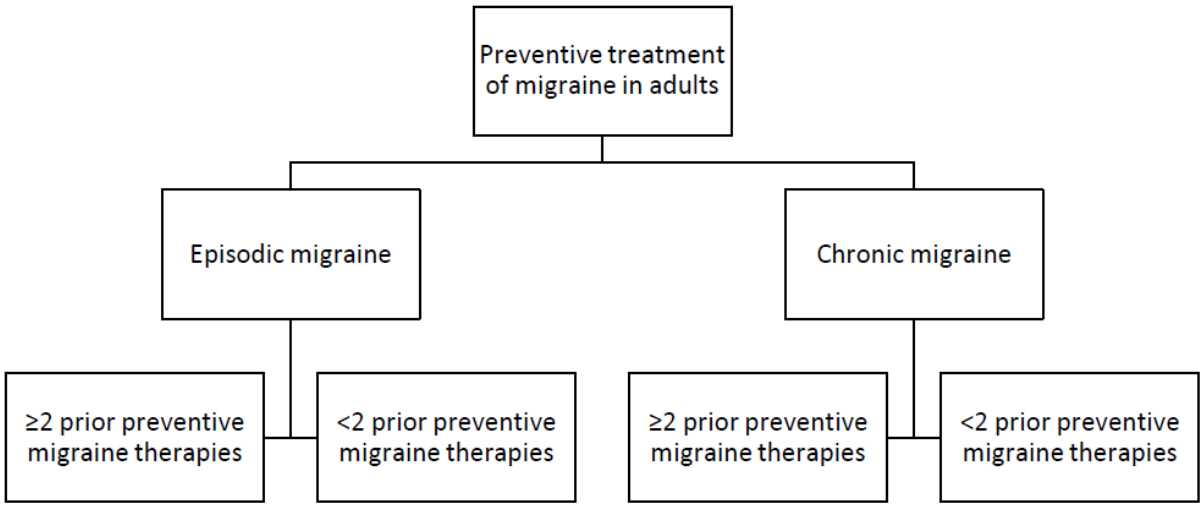
Table 10: Submission Quality

Description	Yes	No	Comments
Population is relevant, with no critical intervention missing, and no relevant outcome missing	☒	☐	
Model has been adequately programmed and has sufficient face validity	☒	☐	The model file is unnecessarily complex and is slow to run (while being within CADTH's runtime requirements).
Model structure is adequate for decision problem	☐	☒	The structure of the model file contained several non-modifiable items. For example, oral comparators could not be added in an analysis that contained other CGRPs, and treatment effect could not be modified beyond 64 weeks.
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis)	☒	☐	
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem	☒	☐	
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough details)	☒	☐	Several referencing errors were noted in the pharmacoeconomic submission, with discrepancies between the Excel model and the pharmacoeconomic report.

CGRP = calcitonin gene–related peptide.

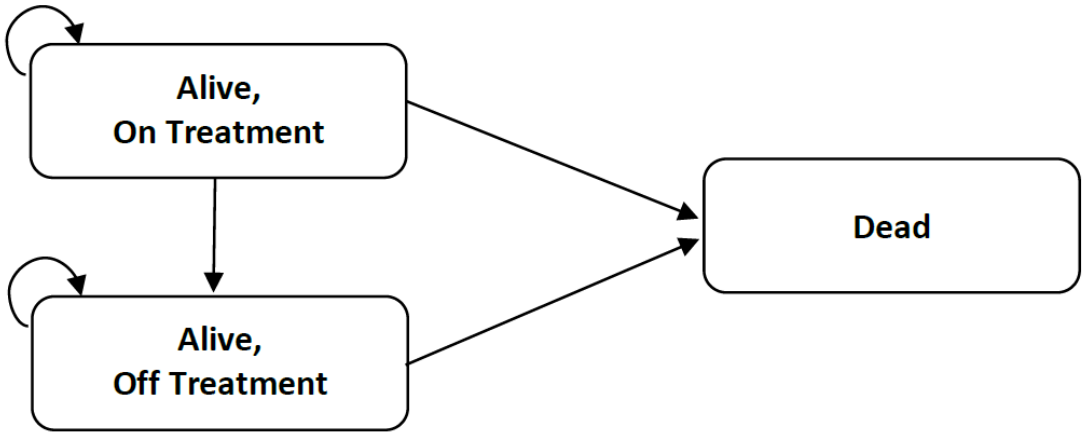
Appendix 3: Additional Information on the Submitted Economic Evaluation

Figure 1: Target Population



Source: Sponsor's pharmacoeconomic submission.[3]

Figure 2: Model Structure

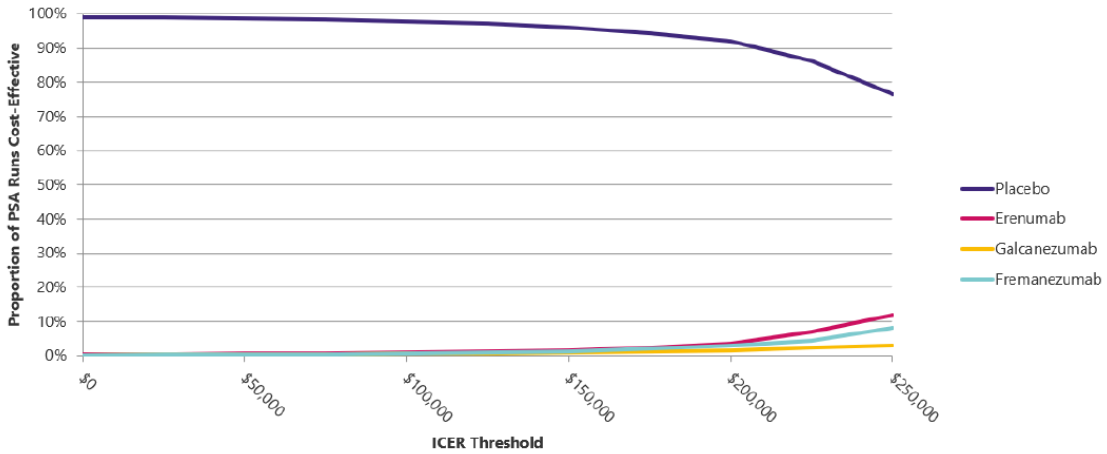


Source: Sponsor's pharmacoeconomic submission.[3]

Detailed Results of the Sponsor's Base Case

The following section provides additional information about the analyses submitted by the sponsor for patients with EM or CM, stratified by the number of prior preventive treatments.

Figure 3: Cost-Effectiveness Acceptability Curve for the Probabilistic Base-Case Analysis — Episodic Migraine, Fewer Than 2 Prior Preventive Migraine Therapies



ICER = incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analysis.

Source: Sponsor's pharmacoeconomic submission.[3]

Table 11: Disaggregated Summary of Sponsor's Results — Episodic Migraine, Fewer Than 2 Prior Preventive Migraine Therapies

Drug	Placebo[a]	Fremanezumab	Erenumab	Galcanezumab
Discounted LYs				
Total	9.20	9.20	9.20	9.20
Discounted QALYs				
Total	6.022	6.062	6.057	6.063
On-treatment	0	1.345	1.340	1.347
Off-treatment	6.022	4.717	4.717	4.716
Trial period	0.150	0.152	0.152	0.152
Post-trial period	5.872	5.910	5.905	5.911
Discounted costs ($)				
Total	42,442	56,330	55,153	57,949
Treatment costs	0	15,222	13,850	16,849
Drug costs	0	15,222	13,850	16,849
Administration costs	0	0	0	0
Migraine-related costs[b]	42,442	41,108	41,304	41,099

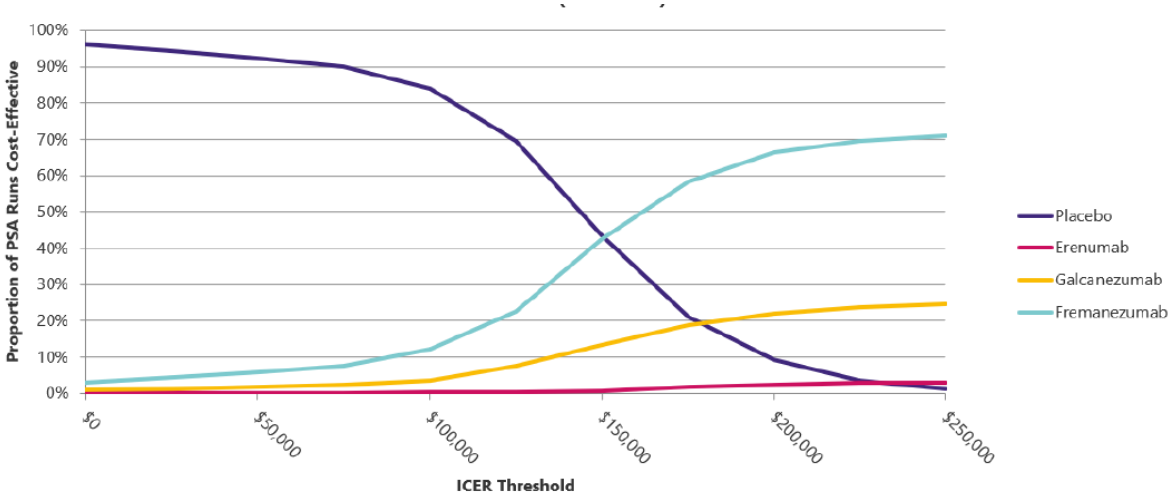
LY = life-year; QALY = quality-adjusted life-year.

[a] Placebo comprised acute migraine-specific and nonspecific treatments.

[b] Includes health care resource use and acute migraine-specific and nonspecific treatments.

Source: Sponsor's pharmacoeconomic submission.[3]

Figure 4: Cost-Effectiveness Acceptability Curve for the Probabilistic Base-Case Analysis — Episodic Migraine, 2 or More Prior Preventive Migraine Therapies



ICER = incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analysis.

Source: Sponsor's pharmacoeconomic submission.[3]

Table 12: Disaggregated Summary of Sponsor's Results — Episodic Migraine, 2 or More Prior Preventive Migraine Therapies

Drug	Placebo[a]	Fremanezumab	Erenumab	Galcanezumab
Discounted LYs				
Total	9.18	9.18	9.18	9.18
Discounted QALYs				
Total	6.004	6.093	6.049	6.075
On-treatment	0	1.392	1.349	1.375
Off-treatment	6.004	4.701	4.700	4.700
Trial period	0.150	0.155	0.152	0.154
Post-trial period	5.855	5.938	5.897	5.921
Discounted costs ($)				
Total	42,319	54,517	54,684	56,815
Treatment costs	0	15,207	13,836	16,833
Drug costs	0	15,207	13,836	16,833
Administration costs	0	0	0	0
Migraine-related costs[a]	42,319	39,310	40,849	39,982

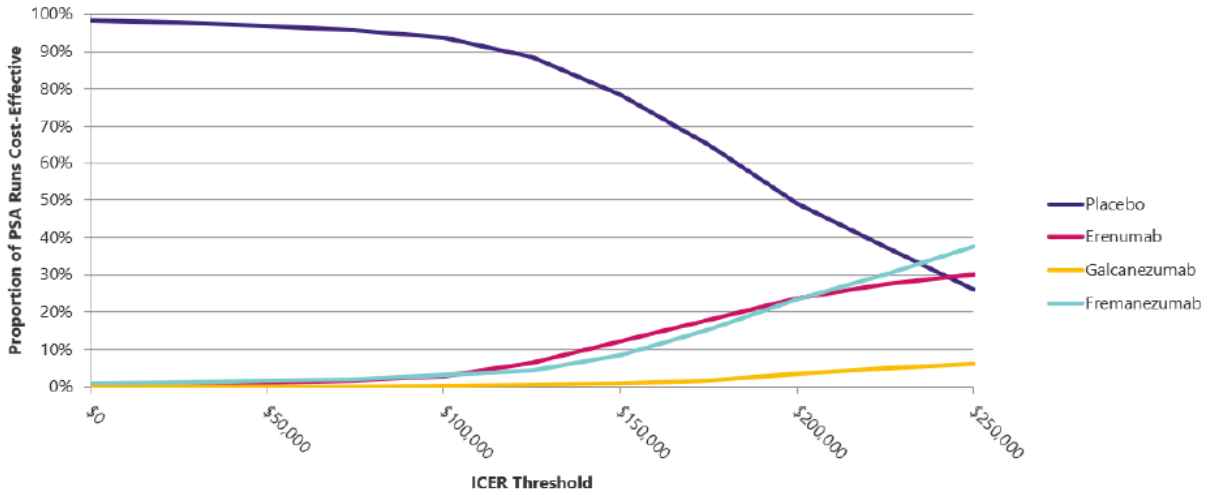
LY = life-year; QALY = quality-adjusted life-year.

[a] Placebo comprised acute migraine-specific and nonspecific treatments.

[b] Includes health care resource use and acute migraine-specific and nonspecific treatments.

Source: Sponsor's pharmacoeconomic submission.[3]

Figure 5: Cost-Effectiveness Acceptability Curve for the Probabilistic Base-Case Analysis — Chronic Migraine, Fewer Than 2 Prior Preventive Migraine Therapies



ICER = incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analysis.

Source: Sponsor's pharmacoeconomic submission.[3]

Table 13: Disaggregated Summary of Sponsor's Results — Chronic Migraine, Fewer Than 2 Prior Preventive Migraine Therapies

Drug	Placebo[a]	Fremanezumab	Erenumab	Galcanezumab
Discounted LYs				
Total	9.21	9.21	9.21	9.21
Discounted QALYs				
Total	4.805	4.862	4.847	4.822
On-treatment	0	1.099	1.084	1.058
Off-treatment	4.805	3.764	3.763	3.764
Trial period	0.118	0.121	0.120	0.119
Post-trial period	4.687	4.741	4.727	4.703
Discounted costs ($)				
Total	80,712	94,158	93,310	97,072
Treatment costs	0	15,251	13,874	16,866
Drug costs	0	15,251	13,874	16,866
Administration costs	0	0	0	0
Migraine-related costs[b]	80,712	78,907	79,436	80,206

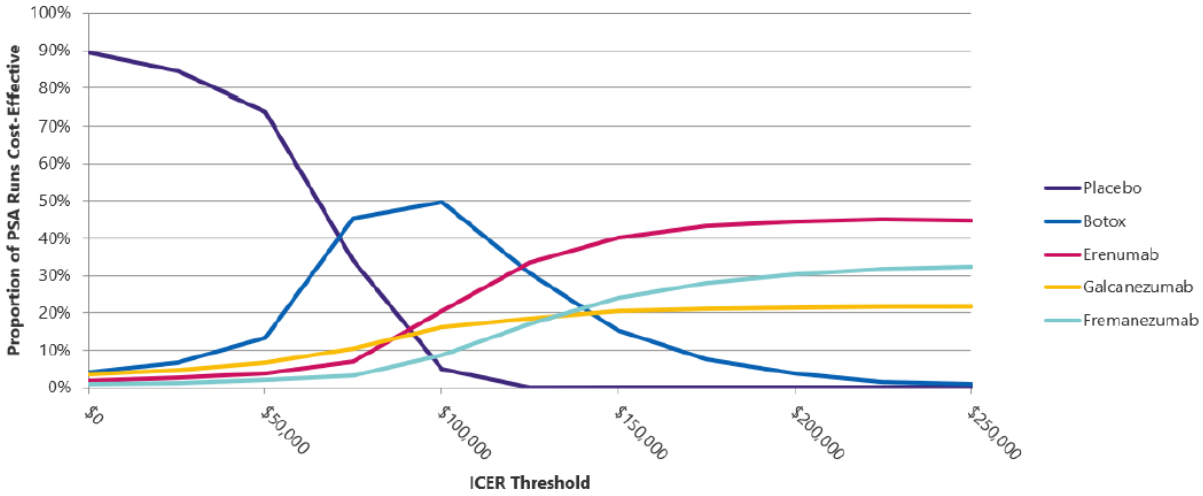
LY = life-year; QALY = quality-adjusted life-year.

[a] Placebo comprised acute migraine-specific and nonspecific treatments.

[b] Includes health care resource use and acute migraine-specific and nonspecific treatments.

Source: Sponsor's pharmacoeconomic submission.[3]

Figure 6: Cost-Effectiveness Acceptability Curve for the Probabilistic Base-Case Analysis — Chronic Migraine, 2 or More Prior Preventive Migraine Therapies



ICER = incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analysis.

Source: Sponsor's pharmacoeconomic submission.[3]

Table 14: Disaggregated Summary of Sponsor's Results — Chronic Migraine, 2 or More Prior Preventive Migraine Therapies

Drug	Placebo[a]	Fremanezumab	Erenumab	Galcanezumab	Onabotulinumtoxin A
Discounted LYs					
Total	9.18	9.18	9.18	9.18	9.18
Discounted QALYs					
Total	4.788	4.902	4.901	4.928	4.829
On-treatment	0	1.154	1.154	1.180	0.535
Off-treatment	4.788	3.748	3.747	3.748	4.294
Trial period	0.118	0.125	0.125	0.126	0.124
Post-trial period	4.670	4.777	4.776	4.802	4.705
Discounted costs ($)					
Total	80,424	92,073	90,749	92,869	82,568
Treatment costs	0	15,232	13,857	16,846	3,446
Drug costs	0	15,232	13,857	16,846	2,950
Administration costs	0	0	0	0	496
Migraine-related costs[b]	80,424	76,841	76,892	76,023	79,122

LY = life-year; QALY = quality-adjusted life-year.

[a] Placebo comprised acute migraine-specific and nonspecific treatments.

[b] Includes health care resource use and acute migraine-specific and nonspecific treatments.

Source: Sponsor's pharmacoeconomic submission.[3]

Table 15: Summary of the Sponsor's Economic Evaluation Results — Scenario Analyses Including Oral Prophylactic Treatments, By Migraine Classification

Drug[a]	Total costs ($)	Total QALYs	Sequential ICER ($/QALY)
Episodic migraine, < 2 prior preventive therapies			
Amitriptyline	42,249	6.013	—
Propranolol	42,255	6.014	8,730
Topiramate	42,287	6.014	Dominated
Placebo	42,451	6.006	Dominated
Fremanezumab	56,377	6.046	434,870
Episodic migraine, 2 prior preventive therapies			
Amitriptyline	42,126	5.996	—
Propranolol	42,146	5.996	29,544
Topiramate	42,164	5.996	Dominated
Placebo	42,328	5.989	Dominated
Fremanezumab	54,572	6.078	152,977
Chronic migraine, < 2 prior preventive therapies			
Topiramate	85,660	4.812	—
Amitriptyline	85,699	4.809	Dominated
Propranolol	85,702	4.810	Dominated
Placebo	85,814	4.805	Dominated
Fremanezumab	99,165	4.862	266,538
Chronic migraine, 2 prior preventive therapies			
Topiramate	80,298	4.781	—
Amitriptyline	80,339	4.779	Dominated
Propranolol	80,345	4.779	Dominated
Placebo	80,443	4.775	Dominated
Botox	82,588	4.817	64,911
Fremanezumab	92,062	4.889	131,647

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Note: The submitted analysis is based on the publicly available prices of the comparator treatments.

[a] Effectiveness estimates for topiramate, amitriptyline, and propranolol were obtained from an economic evaluation of anti-CGRPs,[23] and the effectiveness of amitriptyline and propranolol were assumed to be constant across all 4 assessed migraine subtypes (EM and CM migraine ≥ 2 and < 2 prior therapies).[3] Effectiveness estimates for fremanezumab were based on sponsor-provided NMAs.[4]

Source: Sponsor's pharmacoeconomic submission.[3]

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

Detailed Results of CADTH Base Case

Table 16: Summary of the CADTH Reanalysis Results — Episodic Migraine, Fewer Than 2 Prior Preventive Migraine Therapies

Stepped analysis	Drug	Total costs ($)	Total QALYs	ICER ($/QALYs)
Sponsor's base case	BSC	42,442	6.022	—
	Fremanezumab	56,330	6.062	348,676
CADTH reanalysis 1	BSC	8,470	6.008	—
	Fremanezumab	23,455	6.048	373,437
CADTH reanalysis 2	BSC	22,828	3.131	—
	Fremanezumab	35,705	3.168	348,654
CADTH base case (reanalysis 1+2+3[a])	BSC	4,397	3.127	—
	Fremanezumab	18,263	3.163	377,664

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

[a] CADTH reanalysis 3 consisted of changing the comparator in the model to BSC and did not involve changes to model inputs; as a result, there is no change to the costs, QALYs, or ICER related to reanalysis 3.

Table 17: Summary of the CADTH Reanalysis Results — Episodic Migraine, 2 or More Prior Preventive Migraine Therapies

Stepped analysis	Drug	Total costs ($)	Total QALYs	ICER ($/QALYs)
Sponsor's base case	BSC	42,319	6.004	—
	Fremanezumab	54,517	6.093	138,122
CADTH reanalysis 1	BSC	8,462	5.985	—
	Fremanezumab	23,159	6.074	165,484
CADTH reanalysis 2	BSC	21,407	3.130	—
	Fremanezumab	32,846	3.213	139,228
CADTH base case (reanalysis 1+2+3[a])	BSC	4,396	3.118	—
	Fremanezumab	17,967	3.201	164,243

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

[a] CADTH reanalysis 3 consisted of changing the comparator in the model to BSC and did not involve changes to model inputs; as a result, there is no change to the costs, QALYs, or ICER related to reanalysis 3.

Table 18: Summary of the CADTH Reanalysis Results — Chronic Migraine, Fewer Than 2 Prior Preventive Migraine Therapies

Stepped analysis	Drug	Total costs ($)	Total QALYs	ICER ($/QALYs)
Sponsor's base case	BSC	80,712	4.805	—
	Fremanezumab	94,158	4.862	297,192
CADTH reanalysis 1	BSC	15,853	4.795	—
	Fremanezumab	30,708	4.852	258,897
CADTH reanalysis 2	BSC	42,162	2.498	—
	Fremanezumab	54,599	2.551	236,856
CADTH base case (reanalysis 1+2+3[a])	BSC	8,301	2.503	—
	Fremanezumab	22,053	2.556	257,610

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

[a] CADTH reanalysis 3 consisted of changing the comparator in the model to BSC and did not involve changes to model inputs; as a result, there is no change to the costs, QALYs, or ICER related to reanalysis 3.

Table 19: Summary of the CADTH Reanalysis Results — Chronic Migraine, More Than 2 Prior Preventive Migraine Therapies

Stepped analysis	Drug	Total costs ($)	Total QALYs	ICER ($/QALYs)
Sponsor's base case	BSC	80,424	4.788	—
	Fremanezumab	92,073	4.902	102,184
CADTH reanalysis 1	BSC	15,860	4.776	—
	Fremanezumab	30,328	4.890	127,594
CADTH reanalysis 2	BSC	40,555	2.493	—
	Fremanezumab	51,451	2.598	103,714
CADTH base case (reanalysis 1+2+3[a])	BSC	8,247	2.492	—
	Fremanezumab	21,683	2.596	128,950

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

[a] CADTH reanalysis 3 consisted of changing the comparator in the model to BSC and did not involve changes to model inputs; as a result, there is no change to the costs, QALYs, or ICER related to reanalysis 3.

Table 20: Disaggregated Summary of CADTH's Economic Evaluation Results — Episodic Migraine, Fewer Than 2 Prior Preventive Migraine Therapies

Parameter	BSC	Fremanezumab	Incremental
Discounted LYs			
Total	4.79	4.79	0
Discounted QALYs			
Total	3.127	3.163	0.037
By health state			
On-treatment	0	1.241	1.241
Off-treatment	3.127	1.922	–1.204
Trial period[a]	0.149	0.152	0.002
Post-trial period	2.977	3.012	0.034
Discounted costs ($)			
Total	4,397	18,263	13,865

Parameter	BSC	Fremanezumab	Incremental
Drug costs	0	14,087	14,087
Administration	0	0	0
Migraine-related costs[b]	4,397	4,176	–222
ICER ($/QALY)	377,664		

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year.

[a] 12 weeks.

[b] Includes health care resource use and acute migraine-specific and nonspecific treatments.

Table 21: Disaggregated Summary of CADTH's Economic Evaluation Results — Episodic Migraine, 2 or More Prior Preventive Migraine Therapies

Parameter	BSC	Fremanezumab	Incremental
Discounted LYs			
Total	4.78	4.78	0
Discounted QALYs			
Total	3.118	3.201	0.083
By health state			
On-treatment	0	1.284	1.284
Off-treatment	3.118	1.917	–1.201
Trial period[a]	0.149	0.154	0.005
Post-trial period	2.969	3.046	0.077
Discounted costs ($)			
Total	4,396	17,967	13,571
Drug costs	0	14,071	14,071
Administration	0	0	
Migraine-related costs[b]	4,396	3,896	–500
ICER ($/QALY)	164,243		

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year.

[a] 12 weeks.

[b] Includes health care resource use and acute migraine-specific and nonspecific treatments.

Table 22: Disaggregated Summary of CADTH's Economic Evaluation Results — Chronic Migraine, Fewer Than 2 Prior Preventive Migraine Therapies

Parameter	BSC	Fremanezumab	Incremental
Discounted LYs			
Total	4.79	4.79	0
Discounted QALYs			
Total	2.503	2.556	0.053
By health state			
On-Treatment	0	1.017	1.017
Off-Treatment	2.503	1.539	–0.964
Trial Period[a]	0.118	0.121	0.003
Post-Trial Period	2.385	2.435	0.050
Discounted costs ($)			
Total	8,301	22,053	13,752
Drug costs	0	14,099	14,099
Migraine-related costs[b]	8,301	7,953	–348
ICER ($/QALY)	257,610		

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year.

[a] 12 weeks.

[b] Includes health care resource use and acute migraine-specific and nonspecific treatments.

Table 23: Disaggregated Summary of CADTH's Economic Evaluation Results — Chronic Migraine, 2 or More Prior Preventive Migraine Therapies

Parameter	BSC	Fremanezumab	Incremental
Discounted LYs			
Total	4.78	4.78	0
Discounted QALYs			
Total	2.492	2.596	0.104
By health state			
On-treatment	0	1.066	1.066
Off-treatment	2.492	1.531	–0.961
Trial period[a]	0.118	0.125	0.007
Post-trial period	2.374	2.472	0.0.097
Discounted costs ($)			
Total	8,247	21,683	13,436
Drug costs	0	14,104	14,104
Migraine-related costs[b]	8,247	7,579	–401
ICER ($/QALY)	128,950		

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year.

[a] 12 weeks.

[b] Includes health care resource use and acute migraine-specific and nonspecific treatments.

Scenario Analyses

Table 24: CADTH Scenario Analyses

	CADTH base case	CADTH scenario
Scenario analyses		
1. Health care resource utilization	Costs related to hospitalization for the treatment of migraine were excluded.	Costs related to hospitalization for the treatment of migraine were included.
2. Treatment effectiveness (effectiveness estimate)	Effectiveness estimates (number of MMDs) were based on sponsor-provided NMAs.[4]	Effectiveness estimates (number of MMDs) were based on direct evidence from FOCUS,[11] HALO EM,[10] or HALO CM.[9]
3. Treatment effectiveness (duration of effect)	A constant treatment effect was assumed from week 12 to the end of the analysis horizon (10 years).	Potential waning of treatment effect was explored by modelling a linear reduction in effect, such that the number of MMDs associated with fremanezumab was eventually equal to that for BSC. Owing to the structure of the sponsor's model, waning was assumed to occur up to week 64, after which the treatment effect was assumed to be constant and equivalent to that associated with BSC. Reviewers noted that there is no evidence to support this treatment waning scenario, and it was implemented to explore the uncertainty in the long-term efficacy of fremanezumab.
4. Time horizon of analysis	5 years	10 years
5. Time horizon of analysis		20 years
6. Comparators	Fremanezumab was compared with BSC	Fremanezumab was compared with BSC, erenumab, and OnaA[b]
7. Comparators		Fremanezumab was compared with BSC, erenumab, galcanezumab, and OnaA[b]
8. Comparators		Fremanezumab was compared with BSC, topiramate, amitriptyline, and propranolol
9. Perspective	Health care payer perspective	Societal perspective (i.e., productivity costs were incorporated)
10. Treatment discontinuation	3.71% per 4-week cycle, adopted from a previous economic evaluation of erenumab[8] and assumed equal for all anti-CGRPs[3]	3% every 12 weeks, as reported by Ashina et al. (2019),[31] in which about 34% of participants had discontinued erenumab after a median exposure of 3.2 years (assumed equal for all anti-CGRPs)

BSC = best supportive care; MMD = monthly migraine day; OnaA = onabotulinumtoxin A.

[a] Response rates at 12 weeks were based on sponsor-provided network meta-analyses.[3,4]

[b] Onabotulinumtoxin A was included as a comparator for CM ³2 prior preventive migraine therapies.

Table 25: CADTH Scenario Analyses Results — Episodic Migraine, Fewer Than 2 Prior Preventive Migraine Therapies

	Therapy	Cost ($)	QALYs	ICER ($/QALY)
1. Health care resource utilization	BSC	22,518	3.130	—
	Fremanezumab	35,345	3.167	348,311
2. Treatment effectiveness (direct evidence)	BSC	4,317	3.150	—
	Fremanezumab	18,193	3.187	378,895
3. Duration of treatment effect	BSC	3,121	3.130	—
	Fremanezumab	17,147	3.141	1,259,465
4. Time horizon (10 year)	BSC	8,470	6.008	—
	Fremanezumab	23,455	6.048	373,437
5. Time horizon (20 year)	BSC	15,566	11.085	—
	Fremanezumab	30,656	11.126	372,616
6. Comparators	BSC	4,397	3.127	—
	Erenumab	17,022	3.158	Extendedly dominated
	Fremanezumab	18,263	3.163	377,664
7. Comparators	BSC	4,397	3.127	—
	Erenumab	17,022	3.158	Extendedly dominated
	Fremanezumab	18,263	3.163	377,664
	Galcanezumab	19,809	3.164	1,616,853
8. Comparators	Amitriptyline	4,366	3.140	—
	BSC	4,380	3.133	Dominated
	Propranolol	4,396	3.141	44,097
	Topiramate	4,420	3.141	Dominated
	Fremanezumab	18,236	3.170	475,516
9. Perspective	BSC	38,482	3.129	—
	Fremanezumab	51,281	3.166	347,367
10. Treatment discontinuation	BSC	4,389	3.130	—
	Fremanezumab	30,970	3.203	364,916

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Table 26: CADTH Scenario Analyses Results — Episodic Migraine, 2 or More Prior Preventive Migraine Therapies

	Therapy	Cost ($)	QALYs	ICER ($/QALY)
1. Health care resource utilization	BSC	22,489	3.126	—
	Fremanezumab	33,745	3.208	137,916
2. Treatment effectiveness (direct evidence)	BSC	4,227	3.142	—
	Fremanezumab	17,877	3.224	166,481
3. Duration of treatment effect	BSC	4,383	3.167	—
	Fremanezumab	18,360	3.140	995,178
4. Time horizon (10 year)	BSC	8,462	5.985	—
	Fremanezumab	23,159	6.074	165,484
5. Time horizon (20 year)	BSC	15,501	10.979	—
	Fremanezumab	30,272	11.068	166,655
6. Comparators	BSC	4,396	3.118	—
	Erenumab	16,967	3.158	Extendedly dominated
	Fremanezumab	17,967	3.201	164,243
7. Comparators	BSC	4,396	3.118	—
	Erenumab	16,967	3.158	Extendedly dominated
	Fremanezumab	17,967	3.201	164,243
	Galcanezumab	19,663	3.182	Dominated
8. Comparators	Amitriptyline	4,372	3.138	—
	BSC	4,386	3.131	Dominated
	Propranolol	4,416	3.138	60,221
	Topiramate	4,427	3.138	Dominated
	Fremanezumab	17,994	3.212	183,691
9. Perspective	BSC	38,470	3.122	—
	Fremanezumab	49,771	3.203	139,001
10. Treatment discontinuation	BSC	4,383	3.126	—
	Fremanezumab	30,402	3.287	161,264

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Table 27: CADTH Scenario Analyses Results — Chronic Migraine, Fewer Than 2 Prior Preventive Migraine Therapies

	Therapy	Cost ($)	QALYs	ICER ($/QALY)
1. Health care resource utilization	BSC	42,813	2.496	—
	Fremanezumab	55,197	2.548	235,116
2. Treatment effectiveness (direct evidence)	BSC	7,850	2.571	—
	Fremanezumab	21,605	2.623	264,908
3. Duration of treatment effect	BSC	8,285	2.496	—
	Fremanezumab	22,225	2.512	875,110
4. Time horizon (10 year)	BSC	15,853	4.795	—
	Fremanezumab	30,708	4.852	258,897
5. Time horizon (20 year)	BSC	29,260	8.850	—

	Therapy	Cost ($)	QALYs	ICER ($/QALY)
	Fremanezumab	44,238	8.908	260,582
6. Comparators	BSC	8,301	2.503	—
	Erenumab	20,864	2.543	Extendedly dominated
	Fremanezumab	22,053	2.556	257,610
7. Comparators	BSC	8,301	2.503	—
	Erenumab	20,864	2.543	Extendedly dominated
	Fremanezumab	22,053	2.556	258,897
	Galcanezumab	23,836	2.518	Dominated
8. Comparators	Amitriptyline	8,250	2.507	—
	BSC	8,259	2.503	Dominated
	Propranolol	8,268	2.508	Extendedly dominated
	Topiramate	8,269	2.510	8,241
	Fremanezumab	22,041	2.556	298,956
9. Perspective	BSC	67,511	2.494	—
	Fremanezumab	78,971	2.547	217,427
10. Treatment discontinuation	BSC	8,285	2.496	—
	Fremanezumab	34,633	2.600	253,099

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Table 28: CADTH Scenario Analyses Results — Chronic Migraine, 2 or More Prior Preventive Migraine Therapies

	Therapy	Cost ($)	QALYs	ICER ($/QALY)
1. Health care resource utilization	BSC	42,746	2.492	—
	Fremanezumab	53,450	2.596	102,464
2. Treatment effectiveness (direct evidence)	BSC	8,589	2.445	—
	Fremanezumab	21,968	2.550	127,480
3. Duration of treatment effect	BSC	8,273	2.492	—
	Fremanezumab	22,127	2.524	436,334
4. Time horizon (10 year)	BSC	15,860	4.776	—
	Fremanezumab	30,328	4.890	127,594
5. Time horizon (20 year)	BSC	28,968	8.761	—
	Fremanezumab	43,590	8.875	128,301
6. Comparators	BSC	8,247	2.492	—
	Erenumab	20,395	2.597	116,021
	Fremanezumab	21,683	2.596	Dominated
7. Comparators	BSC	8,247	2.492	—
	OnaA	11,428	2.534	76,736
	Erenumab	20,395	2.597	Extendedly dominated
	Fremanezumab	21,683	2.596	Dominated
	Galcanezumab	23,059	2.621	132,530
8. Comparators	Amitriptyline	8,296	2.495	—
	BSC	8,305	2.492	Dominated

	Therapy	Cost ($)	QALYs	ICER ($/QALY)
	Propranolol	8,313	2.496	Extendedly dominated
	Topiramate	8,315	2.498	8,148
	Fremanezumab	21,739	2.596	137,221
9. Perspective	BSC	67,397	2.488	—
	Fremanezumab	76,440	2.592	86,622
10. Treatment discontinuation	BSC	8,273	2.492	—
	Fremanezumab	33,937	2.698	124,360

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; OnaA = onabotulinumtoxin A; QALY = quality-adjusted life-year.

Table 29: CADTH Price-Reduction Analyses — Episodic Migraine, Fewer Than 2 Prior Preventive Migraine Therapies

	ICERs for fremanezumab versus BSC ($/QALY)	
Price reduction	**Sponsor base case**	**CADTH reanalysis**
No price reduction	348,676	377,664
10%	310,441	339,440
20%	274,781	302,820
30%	237,629	266,201
40%	204,155	229,581
50%	165,180	192,962
60%	126,660	156,342
70%	91,019	119,723
80%	**53,294**	83,103
90%	17,171	**46,484**

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Table 30: CADTH Price-Reduction Analyses — Episodic Migraine, 2 or More Prior Preventive Migraine Therapies

	ICERs for fremanezumab versus BSC ($/QALY)	
Price reduction	**Sponsor base case**	**CADTH reanalysis**
No price reduction	138,122	164,243
10%	121,495	149,755
20%	103,955	133,244
30%	87,366	116,732
40%	73,573	100,221
50%	**54,355**	83,710
60%	39,170	67,198
70%	NA	**50,687**
80%	NA	34,175
90%	NA	NA

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; NA = not applicable; QALY = quality-adjusted life-year.

Table 31: CADTH Price-Reduction Analyses — Chronic Migraine, Fewer Than 2 Prior Preventive Migraine Therapies

	ICERs for fremanezumab versus BSC ($/QALY)	
Price reduction	**Sponsor base case**	**CADTH reanalysis**
No price reduction	234,051	257,610
10%	209,443	235,064
20%	184,487	209,455
30%	156,204	183,846
40%	130,951	158,236
50%	105,749	132,627
60%	81,098	107,018
70%	**58,029**	81,408
80%	29,954	**55,799**
90%	NA	30,109

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; NA = not applicable; QALY = quality-adjusted life-year.

Table 32: CADTH Price-Reduction Analyses — Chronic Migraine, 2 or More Prior Preventive Migraine Therapies

	ICERs for fremanezumab versus BSC ($/QALY)	
Price reduction	**Sponsor base case**	**CADTH reanalysis**
No price reduction	102,285	128,950
10%	87,544	115,269
20%	76,528	102,369
30%	62,049	89,470
40%	**51,013**	76,571
50%	39,614	63,672
60%	NA	**50,773**
70%	NA	37,873
80%	NA	NA

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; NA = not applicable; QALY = quality-adjusted life-year.

Appendix 5: Submitted Budget Impact Analysis and CADTH Appraisal

Key Take-Aways of the Budget Impact Analysis

- CADTH identified the following key limitations with the sponsor's analysis:
  - The sponsor assumes that only 37% of CM patients (defined as those having 15 or more migraine days per month) have 4 or more migraine days per month.
  - The sponsor's derivation of the eligible population assumes that CM patients are less likely to receive preventive therapy for migraines than EM patients, and, if undiagnosed as having chronic migraines, are not diagnosed as having migraines at all.
  - The effect of anti-CGRP reimbursement on the market share of OnaA is uncertain.
- The sponsor's scenario analysis, including patients with EM, is more in line with the reimbursement request consistent with the Health Canada indication than the sponsor's base-case analysis.
- CADTH reanalyses included revising the proportion of CM patients with 4 or more migraine days per month to 100%, altering the likelihood that CM patients would receive preventive therapy to be equal that of EM, and assuming that CM patients not diagnosed as having CM may be diagnosed as having EM.
  - When only CM patients were considered, CADTH reanalyses reported that the reimbursement of fremanezumab would be associated with a budgetary increase of $210,740 in year 1, $586,331 in year 2, and $1,135,211 in year 3, for a 3-year total incremental cost of $1,932,282.
  - Should fremanezumab be reimbursed as per its Health Canada indication, where patients with 4 or more migraine days a month are eligible, the 3-year total incremental cost is estimated to be $8,304,975.

Summary of Sponsor's Budget Impact Analysis

In the submitted base-case budget impact analysis (BIA), the sponsor assessed the introduction of preventive fremanezumab for the treatment of CM in adult patients, compared with preventive erenumab, OnaA, or oral therapies (Table 33). An additional analysis assessing the introduction of preventive fremanezumab for the treatment of EM or CM, more consistent with the reimbursement request as per the approved indication of migraine prevention in adult patients with at least 4 migraine days per month, was also conducted.[2] The BIA was undertaken from the perspective of a Canadian public payer over a 3-year time horizon (2022 through 2024), using an epidemiological approach. The sponsor included drug acquisition costs, including wastage where applicable, as well as jurisdictionally appropriate mark-ups and dispensing fees. Data for the model were obtained from various sources, including Statistics Canada,[12,32] Institut national d'excellence en santé et en services sociaux (INESSS),[33] published literature,[5,34] and the sponsor's internal data.[35] Key inputs to the BIA are documented in Table 33.

Key assumptions included the following:

- Patients with CM are less likely to receive preventive therapy than patients with EM.
- Fremanezumab will only take market share from erenumab, with a small proportion of OnaA patients switching. Patients receiving oral preventive therapies will not switch.

Table 33: Summary of Key Model Parameters

Parameter	Sponsor's estimate (reported as year 1/year 2/year 3 if appropriate)	
	Chronic migraine	Episodic migraine
Target population		
Proportion of population with migraine Annual population growth	5.3% of men / 13.8% of women[a] 1.3%	
Proportion of migraine population in respective category Percent of patients with > 4 migraine days per month Percent of patients with migraine consulting HCP Percentage consulting HCP and getting diagnosis Percentage with diagnosis receiving preventive therapy Percentage migraine patients covered by public plan	8.8% 37% 40.8% 24.6% 44.4% 35%	91.2% 37% 45.5% 86.7% 66.7% 35%
Number of patients eligible for drug under review (Ontario reported as example)	608/616/624	37,207/37,690/38,180
Market uptake (3 years, chronic migraine population only in base case)		
Uptake (reference scenario) Erenumab (Aimovig) OnaA (Botox) Amitriptyline Propranolol Topiramate Other therapies	[redacted] **31.2%/29.4%/27.5%** **15.7%/14.8%/13.9%** **15.7%/14.8%/13.9%** **22.4%/21.0%/19.7%**	[redacted] **36.7%/36.7%/36.7%** **18.5%/18.5%/18.5%** **18.5%/18.5%/18.5%** **26.3%/26.3%/26.3%**
Uptake (new drug scenario) Fremanezumab (Ajovy) Erenumab (Aimovig) OnaA (Botox) Amitriptyline Propranolol Topiramate Other therapies	[redacted] **31.2%/29.4%/27.5%** **15.7%/14.8%/13.9%** **15.7%/14.8%/13.9%** **22.4%/21.0%/19.7%**	[redacted] **36.6%/36.6%/36.5%** **18.5%/18.4%/18.4%** **18.5%/18.4%/18.4%** **26.2%/26.2%/26.1%**
Cost of treatment (per patient per year of therapy)		
Fremanezumab (Ajovy) Erenumab (Aimovig) OnaA (Botox) Amitriptyline Propranolol Topiramate Other therapies	$7,650 $7,001 $3,600 $96 $166 $216 Average of amitriptyline, propranolol, and topiramate	

HCP = health care provider; OnaA = onabotulinumtoxin A.

[a] Data for other genders were not available.

Summary of the Sponsor's Budget Impact Analysis Results

Results of the sponsor's base case suggested an incremental cost of $13,206, $36,742, and $71,138 in years 1, 2, and 3, respectively, for adult patients with CM, for a total of $121,086 over the 3-year period. When the sponsor considered a scenario in which only patients who had failed 2 or more previous line of preventive therapy were eligible (87% of base case eligible patients), the estimated 3-year incremental cost decreased to $118,684. When all EM (more than 4 migraine days per month) and CM patients are considered eligible, the estimated 3-year incremental cost rises to $7,442,748.

CADTH Appraisal of the Sponsor's Budget Impact Analysis

CADTH identified several key limitations of the sponsor's analysis that have notable implications for the results of the BIA:

- **Derivation of the eligible population:** The sponsor derived the eligible population using several sources which, when combined, lack face validity. First, the sponsor applied an estimate from INESSS[33] that 37% of migraine patients have 4 or more migraine days per month to both the CM and EM patient populations, despite CM patients having 15 or more migraine days per month by definition. Second, by naively combining 2 different sources[5,34] to derive the proportions of patients with CM or EM who seek out a health care provider, receive a diagnosis, and are prescribed preventive treatment for that diagnosis, the sponsor did not adequately model what would happen in a single health care system. CADTH reviewers and clinical expert consultation did not find it plausible that a far lower proportion of CM patients (40.8% seeking a provider × 24.6% receiving a diagnosis × 44.4% receiving preventive therapy = 4.5%) would receive preventive migraine therapy than EM patients (45.5% × 86.7% × 66.7% = 26.3%). Finally, in the scenario including EM patients, which is more representative of fremanezumab's indication and the reimbursement request than the base-case analysis, CM patients who did not receive a CM diagnosis disappeared from the model, rather than having a chance to be diagnosed as EM patients and to still potentially receive preventive treatment.
  - CADTH recalculated the proportion of patients with 4 or more migraine days per month to be 100% of CM patients and 31% of EM, for a total of 37% of the whole population, consistent with the INESSS estimate.
  - CADTH considered that, in the same health care system, CM patients would have at least as much opportunity to receive preventive therapy for migraine as EM patients; thus, the proportions of CM patients consulting a health care provider, receiving a diagnosis, and being prescribed treatment were set to be equal to that of the sponsor's EM population.
  - In the scenario analysis in which EM patients were eligible for treatment with fremanezumab, CADTH redirected CM patients who did not receive a CM diagnosis so that they had the opportunity to be diagnosed as having EM instead; thus, still having a chance to receive preventive therapy. As the proportions of patients seeking care, being diagnosed, and receiving preventive therapy are uncertain, and as many patients responding to a survey reported being dissatisfied with the care they received from their physicians (see Stakeholder Input section), a second scenario analysis was conducted under the same assumptions, except all patients were assumed to seek care, be diagnosed, and be prescribed preventive treatment in proportions equal to those of the sponsor's lower assumptions for the CM population.
- **Impact on OnaA market share uncertain:** The sponsor's analysis assumed that fremanezumab would take market share only from erenumab, with a small proportion ([redacted]) switching from OnaA. In contrast, the clinical expert consulted by CADTH suggested that the proportion of patients receiving OnaA will shrink with the availability of either fremanezumab or erenumab on the market, because they are easier to administer and do

not require travel for treatment, and that the availability of a second anti-CGRP agent will expedite that change.

- While information was insufficient to inform a change in the CADTH base-case reanalysis, in a scenario analysis, CADTH estimated that the 10% of patients using OnaA in the base year will shrink to 9% in year 1, 8.5% in year 2, and 8% by year 3 of the analysis in the reference case (with those patients instead using erenumab), while, in the new drug scenario, it will shrink to 9% in year 1, 8% in year 2, and 7% in year 3 (with those patients proportionally split between erenumab and fremanezumab).

CADTH Reanalyses of the Budget Impact Analysis

CADTH revised the sponsor's submitted analysis by changing the proportion of patients experiencing 4 or more migraine days per month to be consistent with the definition of CM, and by altering the proportions of CM patients seeking care from a health care provider, receiving a diagnosis, and being prescribed prophylactic therapy to be equivalent to the proportions of EM patients doing so (Table 34).

Table 34: CADTH Revisions to the Submitted Budget Impact Analysis

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
1. None		
Changes to derive the CADTH base case		
1. Proportion of patients with 4 or more migraine days per month	CM patients: 37% EM patients: 37%[a]	CM patients: 100% EM patients: 31%[a]
2. Proportion CM patients receiving diagnosis and therapy equal to that of sponsor's assumptions for EM patients	Proportion seeking HCP: 40.8% Proportion receiving diagnosis: 24.6% Proportion prescribed prophylaxis: 44.4%	Proportion seeking HCP: 45.5% Proportion receiving diagnosis: 86.7% Proportion prescribed prophylaxis: 66.7%
CADTH base case		1 + 2

CM = chronic migraine; HCP: health care provider; EM = episodic migraine.

[a] EM patients are not eligible for prophylactic fremanezumab therapy in either the sponsor's or CADTH base cases. EM patients are considered eligible in some scenario analyses.

The results of the CADTH step-wise reanalysis are presented in summary format in Table 35 and a more detailed breakdown is presented in Table 36. Applying these changes increased the 3-year total budget impact to $1,932,282 should only CM patients be considered eligible to receive fremanezumab.

Table 35: Summary of the CADTH Reanalyses of the Budget Impact Analysis

Stepped analysis	Three-year total
Submitted base case	$121,086
CADTH reanalysis 1 – Proportion patients ≥ 4 migraine days	$327,260
CADTH reanalysis 2 – Chronic patients receive diagnosis and prophylaxis at rates consistent with episodic patients	$714,944
CADTH base case	$1,932,282

CADTH also conducted additional scenario analyses (Table 36). Scenario analyses where only CM patients were eligible for fremanezumab, as in the sponsor's and CADTH base cases, included

A. Only patients who have failed at least 2 lines of preventive therapy are part of the eligible population

B. Anti-CGRPs (i.e., erenumab, galcanezumab) would take an increased amount of market share from OnaA as described in the limitations section.

Scenario analyses in which EM patients with 4 or more migraines per month were also eligible for fremanezumab included

C. Patients with EM who would be eligible to receive fremanezumab, similar to the sponsor's scenario, with the exception that CM patients who seek out a health care provider but do not receive a diagnosis of CM could instead be diagnosed with EM

D. As scenario C, except CM and EM patients could seek care, be diagnosed, and receive preventive treatment equal to sponsor's inputs for CM patients rather than EM.

Table 36: Detailed Breakdown of the CADTH Reanalyses of the Budget Impact Analysis

Stepped analysis	Scenario	Year 0 (current situation)	Year 1	Year 2	Year 3	Three-year total
Scenarios where only CM patients were eligible for fremanezumab prophylaxis:						
Submitted base case	Reference	$13,126,152	$13,570,544	$14,206,553	$14,857,712	$42,634,810
	New drug	$13,126,152	$13,583,750	$14,243,296	$14,928,850	$42,755,896
	Budget impact	$0	$13,206	$36,742	$71,138	$121,086
CADTH base case	Reference	$20,772,228	$25,346,464	$32,940,408	$40,737,388	$99,024,260
	New drug	$20,772,228	$25,557,205	$33,526,739	$41,872,599	$100,956,542
	Budget impact	$0	$210,740	$586,331	$1,135,211	$1,932,282
CADTH scenario A: Patients failed ≥ 2 lines of preventive therapy	Reference	$20,427,262	$24,904,587	$32,336,737	$39,967,764	$97,209,088
	New drug	$20,427,262	$25,110,988	$32,911,347	$41,080,709	$99,103,044
	Budget impact	$0	$206,402	$574,609	$1,112,945	$1,893,956
CADTH scenario B: Anti-CGRPs take increased market share from OnaA	Reference	$20,772,228	$27,498,247	$34,749,935	$42,195,028	$104,443,210
	New drug	$20,772,228	$27,735,338	$35,695,301	$43,981,944	$107,412,583
	Budget impact	$0	$237,090	$945,366	$1,786,916	$2,969,373
Scenarios where EM patients with > 4 migraines per month were eligible for fremanezumab prophylaxis:						
Sponsor's submitted alternative analysis including EM patients[a]	Reference	$13,126,152	$13,570,544	$14,206,553	$14,857,712	$42,634,810
	New drug	$13,126,152	$14,782,126	$16,672,714	$18,622,718	$50,077,557
	Budget impact	$0	$1,211,582	$2,466,160	$3,765,006	$7,442,748
CADTH scenario C: EM patients included undiagnosed CM	Reference	$21,205,021	$25,785,031	$33,384,836	$41,187,766	$100,357,633
	New drug	$21,205,021	$27,038,824	$36,085,705	$45,538,078	$108,662,607
	Budget impact	$0	$1,253,793	$2,700,869	$4,350,312	$8,304,975

Stepped analysis	Scenario	Year 0 (current situation)	Year 1	Year 2	Year 3	Three-year total
patients may receive EM diagnosis[a]						
CADTH scenario D: As scenario C, except probabilities for all patients equal sponsor's CM inputs[a]	Reference	$3,933,623	$4,713,879	$6,005,650	$7,331,893	$18,051,421
	New drug	$3,933,623	$4,959,096	$6,529,715	$8,169,997	$19,658,809
	Budget impact	$0	$245,217	$524,066	$838,104	$1,607,387

CGRP: calcitonin gene–related peptide; BIA = budget impact analysis; CM = chronic migraine; EM = episodic migraine; OnaA = onabotulinumtoxin A.

[a] The sponsor's model was not programmed to report detailed information on the budget impact of scenarios including non-CM patients. Individual annual costs and incremental costs have been assessed for each jurisdiction and summed by CADTH. This total equalled the 3-year incremental cost summarized by the model for the scenario.

Price-Reduction Analyses

A series of price-reduction analyses were conducted to estimate the budget impact of assuming a reduction in the submitted price of fremanezumab, under the sponsor's base case, CADTH base case, and CADTH scenario C (which included EM and CM patients).

Table 37: CADTH Price-Reduction Analyses — Budget Impact Analysis

Price reduction	Three-year incremental cost (savings)		
	Sponsor base case	CADTH base case	CADTH scenario C
No price reduction	$121,086	$1,932,282	$8,304,975
10%	($10,846)	($173,073)	$5,557,013
20%	($142,777)	($2,278,429)	$2,809,052
30%	($274,709)	($4,383,784)	$61,091
40%	($406,641)	($6,489,140)	($2,686,870)
50%	($538,572)	($8,594,495)	($5,434,831)

Issue for Consideration

Exclusion of galcanezumab: A third anti-CGRP comparator (galcanezumab) has received approval for the treatment of migraine from Health Canada.[7] However, at the time of this review, the manufacturer of galcanezumab had not yet submitted it for review to CADTH or INESSS, and, thus, neither the sponsor nor CADTH considered galcanezumab as a comparator that would have public payer market share within the time horizon of this BIA. If galcanezumab is reviewed and reimbursed within the 3 years included in this BIA, the market share of fremanezumab within the anti-CGRP class would likely be reduced, leading to a reduced budget impact of reimbursing any single anti-CGRP comparator.

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