CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

ERENUMAB (AIMOVIG)

(Novartis Pharmaceuticals Canada Inc.)

Indication: For prevention of migraine in adults who have had at least four migraine days monthly

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Abbreviations

AE	adverse event
BSC	best supportive care
CM	chronic migraine
CUA	cost-utility analysis
EM	episodic migraine
IBMS	International Burden of Migraine Study
ICUR	incremental cost-utility ratio
ITC	indirect treatment comparison
MMD	monthly migraine day
MOA	mode of administration
MSQ	Migraine-Specific Quality of Life Questionnaire
OLE	open-label extension
Ona A	onabotulinum toxin A
QALY	quality-adjusted life-year
WTP	willingness-to-pay

Table 1: Summary of the Sponsor's Economic Submission

Drug product	Erenumab injection (Aimovig)
Study question	To assess the cost-effectiveness of erenumab 70 mg and erenumab 140 mg compared with BSC for the prevention of migraine in adults who have: • at least 4 migraine days per month (base case) • at least 8 migraine days per month and who have previously failed at least 2 migraine preventive therapies (reimbursement request)
Type of economic evaluation	Cost-utility analysis
Target population	Base-case analysis: adult patients with at least 4 migraine days per month Reimbursement request: adult patients who have at least 8 migraine days per month and who have previously failed at least 2 migraine preventive therapies
Treatment	Erenumab 70 mg or 140 mg administered subcutaneously, once monthly
Outcome	QALY
Comparator	BSC, consisting of treatment with medications used for acute migraine Ona A in CM patients only
Perspective	Canadian publicly funded health care payer
Time horizon	5 years
Results for base case	Base-case analysis: • ICUR of $89,773 for erenumab 70 mg compared with BSC • ICUR of $84,204 for erenumab 140 mg compared with BSC Sponsor reimbursement request: • ICUR of $63,152 for erenumab 70 mg compared with BSC • ICUR of $46,704 for erenumab 140 mg compared with BSC
Key limitations	• The analysis did not include all relevant comparators; the cost-effectiveness of erenumab compared with other treatments is therefore unknown. • The model was not based on the natural history of migraine and therefore does not allow for an assessment of how improvements or worsening in the natural course of the condition could affect the cost-effectiveness of erenumab. • The effect of erenumab on migraine severity was not incorporated in the cost-utility analysis. • A number of limitations were identified with clinical efficacy inputs. The pooling of trial data to inform efficacy estimates in the EM population was done inappropriately — baseline characteristics were not adjusted for. Additionally, there were limitations in the ITC used to inform efficacy parameters in the comparison with Ona A in CM patients. The ITC did not report on the relative efficacy of erenumab compared with placebo. • Discrepancies were found between the sponsor's frequency estimates for health care resource use and those provided by the clinical expert consulted by CADTH. • Uncertainty exists in the long-term efficacy of erenumab beyond the clinical trials (24 weeks for STRIVE; 12 weeks for LIBERTY and Study 295). • Parameter uncertainty was inadequately explored in the probabilistic analysis. • Health-state utility values were informed by treatment-dependent MMD distributions. • Long-term treatment discontinuation was not informed by the most up-to-date data from the ongoing OLE Study 178 of erenumab. • Results were not reported in a stratified manner by EM and CM subgroups.

CDR estimate(s)	Many limitations could not be addressed by CADTH. The CDR reanalyses adjusted discrepancies in health care resource-use estimates between the sponsor and the clinical expert consulted by CADTH, updated the long-term negative discontinuation rate based on more up-to-date data from the ongoing OLE Study 178, used the same MMD distributions for all treatments to calculate health-state utilities, made the discontinuation rate due to AEs for Ona A the same as for erenumab 140 mg, and removed the utility decrement associated with administration of Ona A. All reanalyses were conducted in EM and CM populations separately (no mixed populations were considered). EM was defined as patients having fewer than 15 monthly headache days, of which 4 to 15 are MMDs, and CM was patients having 15 or more monthly headache days of which 8 or more are MMDs. Results of the reanalyses: • For the EM population, the sequential ICUR for erenumab 140 mg is estimated to be $153,635 per QALY (erenumab 70 mg is extendedly dominated) compared to BSC • For the CM population, the sequential ICUR for erenumab 140 mg is estimated to be $66,359 per QALY (Ona A is dominated and erenumab 70 mg is extendedly dominated) compared to BSC • For the reimbursement request in the EM population, the sequential ICUR for erenumab 140 mg is estimated to be $105,695 per QALY (erenumab 70 mg is extendedly dominated) compared to BSC • For the reimbursement request in the CM population, the sequential ICUR for erenumab 140 mg is estimated to be $39,840 per QALY (erenumab 70 mg and Ona A are extendedly dominated)

AE = adverse event; BSC = best supportive care; CM = chronic migraine; CDR = CADTH Common Drug Review; EM = episodic migraine; ICUR = incremental cost-utility ratio; ITC = indirect treatment comparison; MMD = monthly migraine day; OLE = open-label extension; Ona A = onabotulinum toxin A; QALY = quality-adjusted life-year.

Drug	Erenumab (Aimovig)
Indication	For prevention of migraine in patients who have had at least four migraine days monthly
Reimbursement request	For prevention of migraine in adults with at least eight migraine days monthly and who have failed, are intolerant of, or have a contraindication to at least two migraine prevention therapies
Dosage form(s)	Subcutaneous injection
NOC date	August 1, 2018 (70 mg/mL autoinjector), and April 11, 2019 (140 mg/mL autoinjector)
Sponsor	Novartis Pharmaceuticals Canada Inc.

Executive Summary

Background

Erenumab (Aimovig) is indicated for the prevention of migraine in adults who have at least four migraine days per month.[1] The sponsor's requested reimbursement criteria is for the prevention of migraine in adults who have at least eight migraine days per month and who have previously failed, are intolerant of, or have a contraindication to at least two migraine preventive therapies.[2] The recommended dosage is 70 mg monthly administered by subcutaneous injection, although some patients may benefit from a dose of 140 mg monthly. Erenumab is supplied as a solution for injection in a single-dose pre-filled syringe (70 mg/mL or 140 mg/mL) and a single-dose autoinjector (70 mg/mL or 140 mg/mL).[1] The sponsor's submitted price for erenumab is $532 per 70 mg or 140 mg autoinjector.[2] The pre-filled syringe is not currently marketed in Canada.[3] The annual cost of treatment with erenumab is $6,384 per patient.

The sponsor submitted a cost-utility analysis (CUA) comparing erenumab to best supportive care (BSC) for both the indicated population and the sponsor's reimbursement-request population.[1] In all analyses the sponsor assumed that [redacted]% and [redacted]% of patients received erenumab 70 mg and 140 mg, respectively.[2] The BSC consisted of treatment with acute medications and medical management (i.e., visits to a general practitioner and emergency department visits). Both the base-case and reimbursement-request populations consisted of patients with episodic migraine (EM) and chronic migraine (CM), with EM defined as fewer than 15 monthly headache days, of which four to 15 are monthly migraine days (MMDs), and CM defined as 15 or more monthly headache days, of which eight or more are MMDs.[2] The sponsor also compared erenumab 140 mg with onabotulinum toxin A (Ona A) in a scenario analysis in patients with CM.[2] All patients received BSC regardless of treatment. BSC costs were dependent upon a patient's number of MMDs.[2] The analysis was conducted from the perspective of a Canadian publicly funded health care payer over a five-year time horizon with 12-week cycles.[2] Future costs and benefits were discounted at a rate of 1.5% per annum.[2] The sponsor's submitted model consisted of a decision tree to determine patient response to treatment during a 12-week assessment period, and a Markov model to assess long-term treatment costs and benefits.[2]

The efficacy for erenumab versus BSC was based on clinical trials for erenumab in CM (Study 295) and EM (STRIVE and LIBERTY) patient populations.[4-6] In the comparison with Ona A, the relative efficacy was based on the sponsor's indirect treatment comparison (ITC)

of Ona A with erenumab 140 mg in CM patients who failed to respond to at least three previous treatments and who had not previously taken Ona A.[7] Mortality was based on general population mortality and all patients had an equal mortality risk regardless of treatment or migraine frequency.[2] Utility values were based on pooled Migraine-Specific Quality of Life Questionnaire (MSQ) data collected from two erenumab clinical trials (Study 295 and STRIVE) mapped to the EuroQol 5-Dimensions (EQ-5D) questionnaire.[4,5] Health-state utility values were a function of MMDs. Costs included treatment acquisition costs and the costs of health care resource use.[2] No treatment administration costs were included for erenumab injections as they can be self-administered by the patient at home, and the costs of administration for Ona A were assumed to be paid out of pocket by the patient.[2]

For the indicated base-case population, the sponsor reported probabilistic incremental cost-utility ratios (ICURs) of $89,773 per quality-adjusted life-year (QALY) for erenumab 70 mg compared with BSC and $84,204 per QALY for erenumab 140 mg compared with BSC. In the sequential analysis, erenumab 70 mg was extendedly dominated by BSC and erenumab 140 mg. At a willingness-to-pay (WTP) threshold of $50,000 per QALY, there was a 100% probability that BSC was optimal.[8]

For the sponsor's reimbursement request, the ICUR for erenumab 70 mg compared with BSC was $63,152 per QALY.[8] For erenumab 140 mg compared to BSC, the ICUR was $46,704 per QALY.[8] In the sequential analysis, erenumab 70 mg was extendedly dominated by BSC and erenumab 140 mg.[8] At a WTP threshold of $50,000 per QALY, there was a 57% probability that erenumab 140 mg was optimal.[8]

Summary of Identified Limitations and Key Results

CADTH identified several key limitations with the sponsor's analysis. Comparators with Health Canada indications for migraine prophylaxis, such as flunarizine, pizotyline or pizotifen, and topiramate, were excluded from the analysis. Consequently, the cost-effectiveness of erenumab compared to currently used treatments is unknown. The sponsor accounted for the reduction in MMD frequency but did not consider the impact of treatment on migraine severity, which would likely have an effect on patients' quality of life and the cost-effectiveness of erenumab. Additionally, the economic analysis did not account for the natural history of migraine, and the impact of this omission on the cost-effectiveness of erenumab is unknown.

In the sponsor's model, a mixed population of patients with EM and those with CM was considered, which added uncertainty to the results and did not permit an understanding of the cost-effectiveness of erenumab within these populations. An approach that stratifies results by relevant subgroups is recommended in the CADTH economic guidelines.[9] Additionally, the estimates of the proportions of EM and CM patients in the indication and reimbursement request were uncertain.

The sponsor pooled efficacy data from STRIVE and LIBERTY to inform efficacy calculations for the EM population. The approach to pooling the data was inappropriate as the trial populations were not homogenous and no adjustment was made to account for differences in sample sizes or baseline characteristics. The inclusion criteria for the sponsor's ITC comparing erenumab 140 mg with Ona A lacked transparency and there were substantial differences in the responses observed in the placebo arms of the trials, limiting the validity of the ITC results. Adverse event (AE) discontinuation rates for Ona A were reportedly derived from the ITC, but the ITC did not appear to examine AEs in the report provided by the sponsor. The sponsor used the open-label extension (OLE) Study 178 to derive the long-

term discontinuation rates for all treatments and to justify its assumption that patients remaining on erenumab maintained their reduction in MMDs without treatment waning. CADTH noted limitations in the interpretations of Study 178 OLE data for erenumab, including the lack of a control group, a protocol amendment allowing for dose-switching from erenumab 70 mg to erenumab 140 mg, and a lack of individual patient data to accompany the dose-switching. Additionally, more up-to-date data from the ongoing Study 178 were not used to inform long-term discontinuation rates.

Health-state utility values used by the sponsor in the model were mapped to the EQ-5D from MSQ data collected from Study 295 and STRIVE. These were derived using algorithms that used definitions of EM and CM that differed from those used by the sponsor.[10] Additionally, the sponsor did not appropriately justify the selection of studies used to pool MSQ data. The sponsor's model structure was inappropriate in that different distributions of MMDs were applied to the same health state for different treatments, resulting in different utility values for the same health state for different treatments.

CADTH was unable to address the following limitations: the exclusion of key comparators from the analysis; the model's failure to account for migraine severity; the failure to incorporate the natural history of migraine into the model; limitations in the sponsor's ITC; inappropriate pooling of trial data; and uncertainty regarding the long-term efficacy of erenumab. CADTH did account for the following in the reanalyses: uncertainty in the frequency of health care resource use; updated long-term negative discontinuation rates based on the most up-to-date available data from the ongoing OLE Study 178; use of erenumab 140 mg MMD treatment distributions to calculate health-state utility values for all comparators; assuming that the discontinuation rate due to AEs for Ona A was the same as for erenumab 140 mg; and removal of the utility decrement associated with the mode of administration for Ona A reflecting the experience of clinical experts.

For the CADTH base case, in the EM population, erenumab 140 mg was associated with a sequential ICUR of $153,635 per QALY compared to BSC (erenumab 70 mg was extendedly dominated). At a WTP threshold of $50,000 per QALY, there was a 100% probability of BSC being optimal. In the CM population, erenumab 140 mg was associated with a sequential ICUR of $66,359 per QALY versus BSC (Ona A was dominated and erenumab 70 mg was extendedly dominated). At a WTP threshold of $50,000 per QALY, there was an 83% probability of BSC being optimal, and the probabilities that erenumab 140 mg, erenumab 70 mg, and Ona A were optimal were 10%, 6%, and 1%, respectively).

In the CADTH reanalyses for the reimbursement request, for the EM population, erenumab 140 mg had a sequential ICUR of $105,695 per QALY versus BSC (erenumab 70 mg was extendedly dominated). At a WTP threshold of $50,000 per QALY, there was a 100% probability that BSC was optimal. For the CM population, erenumab 140 mg had a sequential ICUR of $39,840 per QALY compared with BSC (erenumab 70 mg and Ona A were extendedly dominated). At a WTP threshold of $50,000 per QALY, there was an 55% probability that erenumab 140 mg was optimal, and the probabilities that BSC, erenumab 70 mg, and Ona A were optimal were 17%, 17%, and 11%, respectively).

In the base-case EM population, a price reduction of 64% is required for erenumab 140 mg to be considered cost-effective at a WTP threshold of $50,000 per QALY. In the base-case CM population, a price reduction of 22% is required for erenumab 140 mg to be considered cost-effective at a WTP threshold of $50,000 per QALY. In the reimbursement-request EM population, a price reduction of 49% is required for erenumab 140 mg to be considered cost-effective at a WTP threshold of $50,000 per QALY. In the reimbursement-request CM

population, no price reductions are required for erenumab 140 mg to be considered cost-effective at a WTP threshold of $50,000 per QALY.

Conclusions

In all populations in all reanalyses of both the indication and reimbursement request, erenumab 70 mg was extendedly dominated and erenumab 140 mg was more costly and more effective than BSC. Erenumab 140 mg appeared to be more cost-effective in the CM population than in the EM population. For patients in the indicated population with CM, the ICUR for erenumab 140 mg compared to BSC was $66,359 per QALY, and for patients with EM the ICUR for erenumab 140 mg was $153,635 per QALY. In the reimbursement-request population, erenumab 140 mg was associated with an ICUR of $39,840 per QALY in the CM population and $105,695 per QALY in the EM population, when compared with BSC.

For erenumab 140 mg to be considered cost-effective at a WTP threshold of $50,000 per QALY, price reductions are required as follows: for EM patients a price reduction of 64% and for CM patients a reduction of 22% would be required; in the reimbursement population, a 49% price reduction would be required for EM patients, while no price reduction would be required for CM patients. In all CADTH reanalyses, erenumab 70 mg was never optimal.

Information on the Pharmacoeconomic Submission

Summary of the Sponsor's Pharmacoeconomic Submission

The sponsor submitted a CUA comparing erenumab 70 mg and erenumab 140 mg with best BSC in both the indicated population and the sponsor's reimbursement-request population.[2] The indicated base-case population was adults who have at least four MMDs.[2] The sponsor's reimbursement-request population was adults with at least eight MMDs who have previously failed, are intolerant of, or have a contraindication to at least two migraine preventive therapies.[2] Patients with both EM and CM were included within the indicated and reimbursement-request populations.[2] Patients with EM have fewer than 15 monthly headache days and four to 15 MMDs.[2] CM patients have 15 or more monthly headache days and eight or more MMDs.[2] In the indicated population 46% and 54% of patients were assumed to have CM and EM, respectively, based on data from the CHORD study,[11] which examined the clinical characteristics of Canadian patients referred to neurologists specializing in managing headaches.[11] In the reimbursement-request population, 68% and 32% of patients were assumed to have CM and EM, respectively, given the midpoint between two estimates of the percentage of migraine patients with CM.[12,13] The sponsor compared erenumab 140 mg to Ona A in CM patients as a scenario analysis.[2]

In the CUA, all patients received BSC, including patients who received erenumab or Ona A.[2] The CUA was conducted from the perspective of a Canadian publicly funded health care payer over a five-year time horizon using 12-week cycles that are half-cycle corrected.[2] Costs and QALYs were discounted at a rate of 1.5% per annum.[2] The sponsor stated that the model population reflected the baseline characteristics observed in the STRIVE clinical trial (82.8% female, average age: 42 years).[5]

The pharmacoeconomic model employed a decision tree to assess an initial three-month period and a Markov model to represent the post-assessment period (Figure 1).[2] The model assessed changes in MMDs based on treatment received and the baseline distribution of MMDs.[2] Given a patient's baseline number of MMDs and the number of MMDs following the three-month assessment period, patients were classified as responders or nonresponders to treatment.[2] Response was defined as a 50% reduction in MMDs from the baseline to the end of the assessment period.[2] In the post-assessment period, nonresponders entered the Markov model in the negative discontinuation health state and were assumed to receive only BSC for the remainder of the time horizon.[2] Responders in the decision tree could enter the Markov model in the "on treatment" or "negative discontinuation" health states.[2] Responders in the on-treatment state were assumed to maintain the reduced number of MMDs observed in the assessment period for the entire model time horizon (i.e., there was no future gain or waning of treatment effects) based on preliminary results of the OLE Study 178.[14] Responders could discontinue treatment due to AEs in the first 24 weeks based on information from the erenumab clinical trials and an ITC for Ona A.[4,5,7] After 24 weeks, those in the on-treatment health state could remain on treatment or discontinue due to all causes and move to the negative discontinuation state at a rate of 2.38% per cycle, based on all-cause discontinuation rates observed in preliminary findings from Study 178.[14] Patients in the negative discontinuation state reverted to their MMD baseline, which was the same for all patients regardless of treatment.[2] General population mortality was used to estimate mortality, and all patients had an equal risk of transitioning to the death state, regardless of treatment or MMD frequency.[2]

The efficacy of both erenumab and BSC in terms of proportion of patients with a 50% reduction in MMDs was derived using data from Study 295 patients with CM and the pooled results of the STRIVE and LIBERTY trials in patients with EM.[4-6] Statistical models were developed to describe the distribution of MMDs in Study 295, STRIVE, and LIBERTY for all patients at baseline, all patients at 12 weeks, and all patients at 24 weeks, as well as distributions of MMDs in responders at 12 and 24 weeks and nonresponders at 12 weeks in all treatment arms.[2] In the scenario analysis in the CM population that compared erenumab with Ona A, the sponsor used relative efficacy data from an ITC that compared erenumab 140 mg versus Ona A in CM patients who failed to respond to at least three prior treatments.[7] The ITC was conducted using data from Study 295 and two pivotal trials for Ona A (PREEMPT 1 and PREEMPT 2).[4]

The sponsor established a mean utility value associated with each health state based on the distribution of patients across the number of MMDs in each health state.[2] Migraine Specific Quality-of-life Questionnaire (MSQ) data from Study 295 and STRIVE were mapped to EQ-5D utility values using algorithms published by Gillard et al.[10] Using these data, the sponsor conducted a multi-level regression model for predicting disutilities associated with MMDs to establish EQ-5D utility values as a function of MMDs. To estimate the mean utility value per health state during the assessment period, the distribution of frequencies of MMDs in each treatment group at baseline, as well as in responders and nonresponders, was multiplied by the corresponding utility value for each MMD frequency. Utility decrements were applied to each MMD-specific utility value. These took account of the disutility associated with the mode of administration (MOA) of treatment (only Ona A) and treatment-related AEs (only Ona A and BSC).[2] Utility decrements were derived from a vignette-based time trade-off utility-valuation study in the UK general population and migraine patients.[15] No utility decrements associated with AEs or MOA were applied to the utility values associated with erenumab.

Treatment acquisition costs were based on the sponsor costs for erenumab, and Ontario Drug Benefit formulary prices for Ona A.[2,16] Administration costs were assumed to be zero for both treatments as Ona A administration is often paid by patients out of pocket and there is a Novartis patient support program for initial injection training for self-administration of erenumab.[2] All patients received BSC, and the level of health care management (resource use) received depended on the number of MMDs experienced by patients.[2] Health care resource costs included hospitalizations and emergency room, general practitioner, nurse, and neurologist visits.[2] The frequency of health care resource use was determined by responses from Canadian patients in a global online survey and the Canadian results of the International Burden of Migraine Study (IBMS) of migraine patients.[17,18] Acute medications (triptans and analgesics) were included as part of BSC costs, and a linear regression was used to predict the number of days of treatment with acute medications per month given the number of MMDs.[2] No AE costs were included in the model, given the similar safety profile of erenumab to placebo.[2]

Sponsor's Base Case

Base-case results associated with the indicated population are presented in Table 2. These results were weighted assuming that 46% of patients had CM.[11] Compared to BSC, erenumab 70 mg was associated with a QALY gain of 0.11 at an additional cost of $10,224, resulting in an ICUR of $89,773 per QALY gained.[8] Erenumab 140 mg was associated with a QALY gain of 0.13 at an additional cost of $10,566, resulting in an ICUR of $84,204 compared to BSC.[8] Overall, the sequential results comparing all comparators together demonstrate that erenumab 140 mg was associated with an ICUR of $84,204 per QALY and that erenumab 70 mg was extendedly dominated by BSC and erenumab 140 mg.[8] At a WTP threshold of $50,000 per QALY, there was a 100% probability that BSC was optimal.[8] Erenumab 70 mg was never the optimal treatment option.[8]

Table 2: Summary of Sequential Results of the Sponsor's Base Case Compared to BSC

	Total costs ($)	Total QALYs	Incremental cost ($) vs. BSC	Incremental QALYs vs. BSC	ICUR ($ per QALY) vs. BSC	Sequential ICUR ($ per QALY)
BSC	9,377	3.01				
Erenumab 70 mg	19,601	3.13	10,224	0.11	89,773	Extendedly dominated
Erenumab 140 mg	19,943	3.14	10,566	0.13	84,204	84,204

BSC = best supportive care; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; vs. = versus.

Source: Results from sponsor's updated pharmacoeconomic model.[8]

The results for the sponsor's reimbursement-request population are presented in Table 3. These results were weighted assuming that 68% of patients had CM.[8] Compared to BSC, erenumab 70 mg was associated with a QALY gain of 0.13 at an additional cost of $8,301, resulting in an ICUR of $63,152 per QALY gained.[8] Erenumab 140 mg was associated with a QALY gain of 0.20 at an additional cost of $9,134, resulting in an ICUR of $46,704 compared to BSC.[8] Overall, the sequential results considering all comparators together demonstrated that erenumab 140 mg was associated with an ICUR of $46,704, and that erenumab 70 mg was extendedly dominated by BSC and erenumab 140 mg.[8] At a WTP threshold of $50,000 per QALY, there was a 57% probability that erenumab 140 mg was optimal in the sponsor's reimbursement request.[8] Erenumab 70 mg was never the optimal option.[8]

Table 3: Summary of Sequential Results of the Sponsor's Reimbursement Request Compared to BSC

	Total costs ($)	Total QALYs	Incremental cost ($) vs. BSC	Incremental QALYs vs. BSC	ICUR ($ per QALY) vs. BSC	Sequential ICUR ($ per QALY)
BSC	11,439	2.75				
Erenumab 70 mg	19,740	2.88	8,301	0.13	63,152	Extendedly dominated
Erenumab 140 mg	20,573	2.95	9,134	0.20	46,704	46,704

BSC = best supportive care; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; vs. = versus.

Source: Results from sponsor's updated pharmacoeconomic model.[8]

Summary of Sponsor's Sensitivity Analyses

Erenumab was compared with Ona A in a scenario analysis conducted in CM patients only (Table 15). The sponsor found that Ona A and erenumab 70 mg were extendedly dominated and the ICUR for erenumab 140 mg compared with BSC was $31,414 per QALY.

The sponsor also conducted a number of scenarios in its reimbursement request, including one that explored the effects of varying the time horizon, discount rates, probability of response, utility decrement per MMD, proportion of patients with CM, and the odds ratio for the probability of response for Ona A, including the possibility of positively discontinuing treatment after receiving erenumab for one year.[2] After a 12-week treatment pause during a re-evaluation period, 20% of patients were assumed to positively discontinue treatment as they were assumed to have well-controlled migraine, based on a study of prolonged treatment with Ona A.[19] In this scenario, when patients positively discontinued, they remained in their positive discontinuation state, thereby maintaining the improved frequency of MMDs obtained with treatment for the entire model time horizon while receiving no further treatment.[2] In a scenario analysis conducted by the sponsor from a societal perspective, erenumab 70 mg was dominated in both the base case and the reimbursement request, and erenumab 140 mg was associated with a sequential ICUR of $49,626 and $12,256 for the base case and reimbursement request, respectively.

Results were somewhat sensitive to the probability of response for erenumab, utility decrement per MMD, discount rate, positive discontinuation scenario, odds ratio for the treatment effect of erenumab versus Ona A, and the adoption of a societal perspective.[2]

Limitations of Sponsor's Submission

CADTH identified the following limitations with the sponsor's submission:

- **The analysis does not include all relevant comparators.** In the sponsor's base case and reimbursement criteria, erenumab was compared with BSC only. A comparison with Ona A was made only in a scenario analysis examining CM patients.[2] In addition to Ona A, several other medications, including topiramate, pizotifen, and flunarizine, are indicated by Health Canada for migraine prophylaxis.[20-22] According to CADTH economic guidelines, all interventions currently used and potentially displaced should be identified, and those that decision-makers are currently funding or are commonly used should be included.[9] Comparator selection should not be limited by the availability of data.[9] Although the sponsor rationalized excluding some comparators due to AEs and high discontinuation rates, these events could have been incorporated using the sponsor's model structure.[2] A lack of efficacy data for these products in patients who had failed prior therapies is another justification provided by the sponsor, but these data are not needed for the base case examining the Health Canada indication. Not including all comparators with a Health Canada indication may favour erenumab, as these comparators are associated with much lower annual costs (see Appendix 1). Reviewers were unable to address this limitation, and as such, the cost-effectiveness of erenumab compared to currently used therapies is unknown.
- **Use of health states that do not capture the full course of the condition.** The health states used by the sponsor to assess the cost-effectiveness of erenumab classify patients as responders or nonresponders and as on-treatment or off-treatment based on the probability of patient response to treatment and the frequency of patient migraine attacks.[2] Further, this model structure does not capture other clinically meaningful aspects of the

disease, such as headache severity. According to the clinical expert consulted by CADTH for this review, 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 headaches may not necessarily be associated with a reduction in headache severity. The direction and magnitude of the impact of the model's structure on the cost-effectiveness results for erenumab are unclear.

- **The natural history of migraine disease course was not incorporated in the model.** No natural change in migraine severity or frequency was incorporated in the analysis, which the sponsor notes is a simplifying assumption.[2] Erenumab and BSC patients were classified as responders or nonresponders according to trial data, and responders who remained on treatment for the entire model time horizon maintained the MMD frequency established during the assessment period.[2] Nonresponders remained in the negative discontinuation state and were assumed to have the frequency of MMDs established at the trial baseline for the entire model time horizon.[2] As such, there was no change in the frequency of MMDs for both responders and nonresponders during the post-assessment period. However, according to a clinical expert consulted by CADTH for this review, a patient's migraine disease course may naturally improve or worsen over time. The direction of the impact of not including natural history of migraine on the results of the analysis is unknown.
- **The ITC suffered from limitations.** There is no direct head-to-head evidence for the efficacy of erenumab versus Ona A or oral preventive medications. For the comparison of erenumab with Ona A in the CM population, the sponsor conducted an ITC of erenumab 140 mg and Ona A 155-195 international units, administered as 31 to 39 intramuscular injections in CM patients with at least three treatment failures using data from Study 295 and published data from the PREEMPT 1 and PREEMPT 2 trials for Ona A.[7] No literature search was conducted and the approach to selecting studies for the ITC was not reported. The ITC considered a population different from the indicated population (no previous treatment failure) and the sponsor's reimbursement request (failure of at least two prior preventive therapies) due to a lack of data available in these populations for Ona A. Results of the ITC obtained with erenumab 140 mg were assumed to be the same for erenumab 70 mg.[2] The sponsor was unable to provide an ITC comparing Ona A with both erenumab 70 mg and 140 mg. In Study 295, slightly more patients who had a 50% reduction in MMDs were treated with erenumab 140 mg compared to those treated with erenumab 70 mg (see CADTH clinical review report). If erenumab 140 mg was more efficacious than erenumab 70 mg, then assuming erenumab 70 mg versus Ona A will have the same rate of response as versus erenumab 140 mg will favour erenumab. Additionally, the sponsor reported that the odds ratio for the discontinuation of Ona A due to AEs relative to erenumab was derived from the ITC.[2] However, the ITC did not appear to examine AE frequencies or discontinuation rates.[7]
- **The trial data was inappropriately pooled.** In the sponsor's model, data were pooled to inform both efficacy and utility estimates. To inform efficacy calculations for the EM population, a pooled dataset of STRIVE and LIBERTY was used.[2] LIBERTY is a 12-week randomized controlled trial.[6] STRIVE is a 24-week trial with 24-week randomized data, though response was also assessed at 12 weeks in this trial.[5] An additional 12-week study conducted in EM patients, ARISE, was not included in the data pool.[23]

  For utility estimates, MSQ data from Study 295 and STRIVE were pooled, on the basis of avoiding sparse data.[2] While LIBERTY did not collect MSQ data, this was an outcome considered in ARISE.[23] Justification for the selection of studies used to pool MSQ data was not provided by the sponsor.

When pooling data from different trials, it is necessary to assume homogeneity in the trials' baseline characteristics. However, the pooled trials were not homogenous. STRIVE excluded patients with no therapeutic response to at least two previous treatments, while LIBERTY enrolled patients who failed two to four prior migraine prophylaxis treatments, indicating a clear difference in the patient populations sampled in each trial.[5,6]

To estimate the probability of response in EM patients, the sponsor pooled trial data from STRIVE and LIBERTY by taking the total number of 12-week responders from STRIVE and LIBERTY and dividing the result by the total number of patients.[24] This approach to pooling is inappropriate. Nonrandomized data from STRIVE were used to inform the pool, rather than using the double-blind 24-week outcome.[24] A more appropriate approach to pooling trial data would have been to conduct a meta-analysis of all EM trials in which the proportion of responders for each study would be calculated then weighted based on the sample size. Overall, the approach to pooling did not include all relevant studies, utilized nonrandomized trial data, did not adjust for differences in baseline characteristics, and did not appropriately weight estimates by trial sample size. The effect of inappropriately pooling trial data on the results of the cost-effectiveness analysis is unknown and could not be addressed by CADTH reviewers.

- **Uncertainty in the frequency estimates for direct health care resource use.** A global online study of patients with at least four MMDs was used to estimate the per-cycle resource utilization rates in the model, using responses from Canadian survey participants. To populate visit-frequency estimates for those experiencing zero to three MMDs, estimates were sourced from the Canadian results of the IBMS. According to clinical expert consulted by CADTH for this review, these estimates may overestimate hospitalizations, as migraine patients are rarely admitted to hospital for migraine. Additionally, the expert noted that the estimates may underestimate the frequency of emergency room visits for migraine patients. It was also unclear what role nurse practitioner visits played in patient care and whether these would be mutually exclusive to a general practitioner visit. CADTH reanalyses adjusted the frequency of health care resource use so that it reflected the experience of clinical experts consulted by CADTH for this review.
- **Uncertainty in the long-term treatment efficacy of erenumab.** In the sponsor's model, those who respond to and remain on treatment are assumed to maintain the improved frequency of MMDs achieved in the first 24 weeks for the entire model time horizon.[2] The justification for this assumption is supported by data from Study 178, an ongoing OLE study of patients completing a 12-week placebo-controlled phase II study of erenumab that showed that there was sustained efficacy of erenumab through 64 weeks of follow-up.[2] A clarification provided by the sponsor presented data from the January 2016 data cut of Study 178, including the mean change in MMDs over 60 months, as well as the proportion of patients experiencing a 50% or greater reduction in MMDs at week 64 and at four years.[24] The CADTH clinical review noted that the denominator used in calculating the proportion of patients experiencing a 50% reduction in MMDs at month 60 was unclear. The CADTH clinical review also noted that the ability to draw conclusions regarding sustained erenumab efficacy was limited due to the lack of a control group and the inclusion of a protocol amendment, which saw a switch in dose from erenumab 70 mg to erenumab 140 mg where possible. A lack of patient-level data on the changes to dosing introduced uncertainty to the long-term results. Additionally, efficacy end points in Study 178 were exploratory and did not include statistical testing, making it difficult to interpret results. Overall, the interpretation of long-term efficacy results from Study 178 is significantly limited.

  According to the clinical expert consulted for this review, as much as 20% of patients may stop benefiting from prophylactic treatment. The assumption that treatment effects of

erenumab will be maintained for the entire model time horizon favoured erenumab, given the limited ability to interpret efficacy results from Study 178. A scenario in which the effect of erenumab wanes linearly over the course of the model time horizon to eventually equal the mean MMD frequency experienced by negative discontinuers was explored as a CADTH sensitivity analysis.

There are no data regarding the benefits of erenumab after stopping treatment. As such, CADTH reviewers concluded the positive discontinuation scenario was not appropriate for consideration.

- **Inadequately examined parameter uncertainty.** Reviewers noted that several parameters, including the probability of discontinuing erenumab or BSC due to AEs; the probability of response for erenumab 70 mg, erenumab 140 mg, and BSC; and the proportion of patients in the indication and reimbursement request that had CM, were not appropriately included in the probabilistic analysis. However, the odds ratios comparing the probability of response and the probability of discontinuation of treatment due to AEs for Ona A relative to erenumab was included in the probabilistic analysis. Reviewers were unable to make these rates probabilistic for erenumab. The odds ratio for discontinuing Ona A due to AEs was fixed in the CADTH reanalysis out of fairness because discontinuation rates for the other comparators were also not probabilistic.
- **Uncertainty in health-state utility values.** To estimate health-state utilities, the sponsor established a mean utility value for each health state based on the distribution of patients across the number of MMDs in each health state.[2] The MSQ data from Study 295 and STRIVE were mapped to EQ-5D utility values using an algorithm published by Gillard et al.[10] Using these data, the sponsor conducted a multi-level regression model for predicting disutilities associated with MMDs to establish EQ-5D utility values as a function of MMDs.[2]

  CADTH reviewers noted several limitations with this approach. CADTH economic guidelines do not recommend mapped utilities and the justification for mapping rather than using EQ-5D values from the literature was not provided.[9] As the mapping algorithm established by Gillard et al. use a UK value set, the utility values used in the model do not reflect Canadian preferences.[10] The sponsor applied the EM or CM algorithm to the MSQ data following the definitions provided in the International Classification of Headache Disorders (i.e., EM patients have fewer than 15 monthly headache days, of which four to 14 are MMDs, and EM patients have 15 or more monthly headache days, of which eight or more are MMDs) whereas Gillard et al. defined EM as fewer than 15 monthly headache days and CM as 15 or more monthly headache days.[10,25] Additionally, MSQ data were also available in the ARISE trial, and its exclusion from the pooled analysis was not justified. According to clinical experts consulted by CADTH, the MOA associated with Ona A involves minimal discomfort for a migraine patient, indicating uncertainty in its inclusion in the model. Additionally, the sponsor's approach to deriving health-state utilities by multiplying MMD utility values by treatment-dependent MMD distributions is limited. Because health states should capture all aspects of a disease, there should be no treatment-dependent differences between health states or health-state utilities. A more appropriate approach would have been to use the same MMD distribution to calculate utility values across all health states, a change that was applied in the CADTH reanalysis.
- **The percent of patients discontinuing long-term treatment may be underestimated.** In the sponsor's analysis, responders who continued treatment in the post-assessment period negatively discontinued treatment at a rate of 2.38% every 12 weeks.[2] The probability of discontinuing treatment was based on total rates of discontinuation for all treatments at the November 2014 data cut in the Clinical Study Report of Study 178.[14] As Study 178 is ongoing, updated data have become available. As reported by Ashina et al., 132 of 383

patients discontinued erenumab for all causes after a median exposure among all patients enrolled of 3.2 years.[26] This resulted in a discontinuation probability of approximately 3% every 12 weeks. As this input was used to model the long-term discontinuation of patients from erenumab, reviewers concluded it was appropriate to use data that reflected the longest patient exposure to treatment, and the CADTH reanalysis reflects this updated discontinuation rate.

- **Uncertainty in the estimates of the proportion of CM patients in the indication and reimbursement request.** For the base case and reimbursement request, the sponsor estimated that 46% and 68% of patients in the pooled cohort had CM, respectively.[2] Data from the CHORD study was used to inform the proportion of CM patients in the indicated population.[11] For the reimbursement request, the estimate was taken to be the midpoint of two proportions, one being from the second IBMS, which found that 58.3% of Canadian patients who had reported any previous use of prophylactic treatment had CM, and an estimate from the US of patients on third-line or later therapy that found 77.8% had CM.[12,27] Reviewers found the approach of taking a midpoint estimate of two proportions in different patient populations and in different health care settings to be highly uncertain and unjustified. Additionally, given that erenumab trials were conducted in EM and CM populations separately and that erenumab may exhibit a different treatment effect in these two subgroups, the validity of considering the cost-effectiveness in a mixed EM and CM population is limited. For the CADTH base case, results are presented for EM and CM groups separately, demonstrating the cost-effectiveness of erenumab in each of these populations.

CADTH Common Drug Review Reanalyses

CADTH could not address limitations associated with the lack of consideration of key comparators, migraine severity, natural history of migraine, inappropriate pooling of trial data, uncertain long-term efficacy, and limitations in the ITC.

Several other limitations were addressed.

- Hospitalization and nurse visits were removed from health care resource use as these represent rare occurrences, according to the clinical expert consulted by CADTH for this review. Both the frequency of visits and unit costs of these visits were changed to zero.
- The all-cause long-term negative discontinuation rate was adjusted from 2.38% to 3% to be consistent with the most up-to-date data from Study 178.[26]
- MMD distributions from erenumab 140 mg 12-week responders, 12-week nonresponders and 24-week responders were used when calculating health-state utilities for all treatments for responders, nonresponders, and on-treatment states.
- The odds ratio for discontinuation of Ona A due to AEs relative to erenumab 140 mg was revised to equal 1 in the CM population, reflecting the uncertainty in the sponsor's estimate for this value.
- Removed the MOA decrement for Ona A, reflecting the experience of clinical experts consulted by CADTH.

The first three limitations are considered in CADTH reanalyses of the EM population. For the CM populations, all five limitations are included in the CADTH reanalyses.

CADTH Common Drug Review Reanalyses

For the base-case EM population, compared to BSC, erenumab 140 mg was $10,688 more expensive and yielded 0.07 more QALYs, resulting in an ICUR of $153,635 per QALY gained (Table 4). Erenumab 70 mg was associated with a QALY gain of 0.07 at an additional cost of $10,196, resulting in an ICUR of $165,396 per QALY compared to BSC. Overall, the sequential results considering all comparators together demonstrated that erenumab 140 mg was associated with an ICUR of $153,635 and that erenumab 70 mg was extendedly dominated by BSC and erenumab 140 mg. At a WTP threshold of $50,000 per QALY, there was a 100% probability that BSC was optimal. At a WTP of $100,000 per QALY, there was a 2% probability that erenumab 140 mg was optimal.

For the base case in the CM population, compared to BSC, erenumab 140 mg was $10,044 more expensive and yielded an additional 0.15 QALYs, resulting in an ICUR of $66,359 per QALY gained (Table 5). Erenumab 70 mg yielded an additional 0.14 QALYs at an additional cost of $9,840, resulting in an ICUR of $70,343 per QALY gained, compared to BSC. Ona A was $3,162 more expensive than BSC and yielded 0.02 fewer QALYs, resulting in Ona A being dominated (it was less effective and more expensive) than BSC. Overall, the sequential results considering all comparators together demonstrated that erenumab 140 mg was associated with an ICUR of $66,359 and that erenumab 70 mg was extendedly dominated by BSC and erenumab 140 mg, and Ona A was dominated. At a WTP threshold of $50,000 per QALY, there was an 83% probability that BSC was optimal, and a 10% probability that erenumab 140 mg was optimal.

Table 4: CDR Reanalyses of Limitations of the Indication in the Episodic Migraine Population

	Scenario	Treatment	QALYs	Cost ($)	Sequential ICUR ($ per QALY)
	Base case, submitted by sponsor (mixed population, 46% CM)[a]	BSC	3.01	9,377	
		erenumab 70 mg	3.13	19,601	ED
		erenumab 140 mg	3.14	19,943	84,204
1	Adjusted health care resource-use frequency	BSC	3.32	5,387	
		erenumab 70 mg	3.40	15,995	ED
		erenumab 140 mg	3.40	16,525	133,494
2	Updated all-cause long-term negative discontinuation rate	BSC	3.31	7,038	
		erenumab 70 mg	3.39	17,080	ED
		erenumab 140 mg	3.39	17,591	132,612
3	Making the distributions used to calculate the utilities for all treatments equal to the distributions for erenumab 140 mg	BSC	3.33	6,950	
		erenumab 70 mg	3.39	17,418	ED
		erenumab 140 mg	3.40	17,947	149,667
CADTH base case (1 + 2 + 5)		BSC	3.32	5,424	
		erenumab 70 mg	3.39	15,620	ED
		erenumab 140 mg	3.39	16,112	153,635

BSC = best supportive care; CDR = CADTH Common Drug Review; CM = chronic migraine; ED = extendedly dominated; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

[a] Results presented from the sponsor's base case were weighted, with 46% of the population having CM and 54% of the population having EM. Results from CADTH reanalyses assume a 100% EM population.

Table 5: CDR Reanalyses of Limitations of the Indication in the Chronic Migraine Population

	Scenario	Treatment	QALYs	Cost ($)	Sequential ICUR ($ per QALY)
	Base case, submitted by sponsor (mixed population, 46% CM)[a]	BSC	3.01	9,377	
		erenumab 70 mg	3.13	19,601	ED
		erenumab 140 mg	3.14	19,943	84,204
1	Adjusted health care resource-use frequency	BSC	2.66	9,496	
		Ona A	2.57	12,647	Dominated
		erenumab 70 mg	2.81	19,739	ED
		erenumab 70 mg	2.83	19,948	62,209
2	Updated all-cause long-term negative discontinuation rate	BSC	2.65	12,222	
		Ona A	2.57	15,305	Dominated
		erenumab 70 mg	2.80	21,827	ED
		erenumab 140 mg	2.81	22,009	60,737
3	Making the distributions used to calculate the utilities for all treatments equal to the distributions for erenumab 140 mg	BSC	2.67	12,168	
		Ona A	2.58	15,370	Dominated
		erenumab 70 mg	2.82	22,154	ED
		erenumab 140 mg	2.83	22,327	64,003
4	Rate of discontinuation for AEs for Ona A equal to erenumab	BSC	2.67	12,131	
		Ona A	2.59	15,428	Dominated
		erenumab 70 mg	2.82	22,140	ED
		erenumab 140 mg	2.83	22,307	60,900
5	Removing MOA decrement for Ona A	BSC	2.66	12,199	
		Ona A	2.63	15,398	Dominated
		erenumab 70 mg	2.81	22,176	ED
		erenumab 140 mg	2.83	22,381	60,029
CADTH base case (1 + 2 + 3 + 4 + 5)		BSC	2.66	9,577	
		Ona A	2.64	12,739	Dominated
		erenumab 70 mg	2.80	19,418	ED
		erenumab 140 mg	2.81	19,621	66,359

AE = adverse events; BSC = best supportive care; CDR = CADTH Common Drug Review; CM = chronic migraine; ED: extendedly dominated; ICUR = incremental cost-utility ratio; MOA = mode of administration; Ona A = onabotulinum toxin A; QALY = quality-adjusted life-year.

[a] Results presented from the sponsor's base case were weighted, with 46% of the population having CM and 54% of the population having EM. Results from CADTH reanalyses assume a 100% CM population.

Reimbursement-Request Population

For the sponsor's reimbursement request in the EM population, compared to BSC, erenumab 140 mg was $8,639 more expensive and yielded an additional 0.08 QALYs, resulting in an ICUR of $105,695 per QALY gained (Table 6). Erenumab 70 mg yielded an additional 0.06 QALYs and was $7,479 more expensive, resulting in an ICUR of $135,709 compared to BSC. Overall, the sequential results considering all comparators together

demonstrated that, compared with BSC, erenumab 140 mg was associated with an ICUR of $105,695 and that erenumab 70 mg was extendedly dominated by BSC and erenumab 140 mg. At a WTP threshold of $50,000, the probability of erenumab 140 mg or 70 mg being optimal was 0%. At a WTP of $100,000, there was a 35% probability that erenumab 140 mg was optimal.

For the sponsor's reimbursement request in the CM population, compared to BSC, erenumab 140 mg was $9,197 more expensive and yielded an additional 0.23 QALYs, resulting in an ICUR of $39,840 per QALY gained (Table 7). Erenumab 70 mg yielded an additional 0.19 QALYs and was $8,448 more expensive, resulting in an ICUR of $44,917 compared to BSC. Ona A yielded an additional 0.06 QALYs and was $2,534 more expensive than BSC, resulting in an ICUR of $42,175. In the sequential analysis, erenumab 140 mg had an ICUR of $39,840 compared to BSC (erenumab 70 mg and Ona A were extendedly dominated). At a WTP of $50,000, there was a 55% probability that erenumab 140 mg was optimal. This increased to 76% at a WTP of $100,000.

Table 6: CDR Reanalyses of Limitations of the Reimbursement Request in the Episodic Migraine Population

	Scenario	Treatment	QALYs	Cost ($)	Sequential ICUR ($ per QALY)
	Base case, submitted by sponsor (mixed population, 68% CM)[a]	BSC	2.75	11,439	
		erenumab 70 mg	2.88	19,740	ED
		erenumab 140 mg	2.95	20,573	46,704
1	Adjusted health care resource-use frequency	BSC	3.20	6,102	
		erenumab 70 mg	3.24	13,876	ED
		erenumab 140 mg	3.29	15,058	93,919
2	Updated all-cause long-term negative discontinuation rate	BSC	3.20	7,843	
		erenumab 70 mg	3.24	15,265	ED
		erenumab 140 mg	3.29	16,338	92,994
3	Making the distributions used to calculate the utilities for all treatments equal to the distributions for erenumab 140 mg	BSC	3.21	7,829	
		erenumab 70 mg	3.27	15,544	ED
		erenumab 140 mg	3.30	16,660	102,404
CADTH base case (1 + 2 + 5)		BSC	3.21	6,123	
		erenumab 70 mg	3.26	13,602	ED
		erenumab 140 mg	3.29	14,762	105,695

BSC = best supportive care; CDR = CADTH Common Drug Review; CM = chronic migraine; ED = extendedly dominated; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

[a] Results presented from the sponsor's base case were weighted, with 68% of the population having CM and 32% of the population having EM. Results from CADTH reanalyses assume a 100% EM population.

Table 7: CDR Reanalyses of Limitations of the Reimbursement Request in the Chronic Migraine Population

	Scenario	Treatment	QALYs	Cost ($)	Sequential ICUR ($ per QALY)
	Base case, submitted by sponsor (mixed population, 68% CM)[a]	BSC	2.75	11,439	
		erenumab 70 mg	2.88	19,740	ED
		erenumab 140 mg	2.95	20,573	46,704
1	Adjusted health care resource-use frequency	BSC	2.54	10,275	
		Ona A	2.54	12,779	ED
		erenumab 70 mg	2.73	19,039	ED
		erenumab 140 mg	2.79	19,875	37,910
2	Updated all-cause long-term negative discontinuation rate	BSC	2.53	13,184	
		Ona A	2.54	15,516	ED
		erenumab 70 mg	2.71	21,317	ED
		erenumab 140 mg	2.77	21,993	36,595
3	Making the distributions used to calculate the utilities for all treatments equal to the distributions for erenumab 140 mg	BSC	2.55	13,161	
		Ona A	2.53	15,563	Dominated
		erenumab 70 mg	2.74	21,618	ED
		erenumab 140 mg	2.79	22,328	37,658
4	Rate of discontinuation for AEs for Ona A equal to erenumab	BSC	2.54	13,124	
		Ona A	2.56	15,627	ED
		erenumab 70 mg	2.73	21,600	ED
		erenumab 140 mg	2.79	22,304	36,270
5	Removing MOA decrement for Ona A	BSC	2.54	13,103	
		Ona A	2.59	15,509	ED
		erenumab 70 mg	2.73	21,582	ED
		erenumab 140 mg	2.79	22,286	36,266
CADTH base case (1 + 2 + 3 + 4 + 5)		BSC	2.54	10,314	
		Ona A	2.60	12,847	ED
		erenumab 70 mg	2.73	18,762	ED
		erenumab 140 mg	2.78	19,511	39,840

AE = adverse event; BSC = best supportive care; CDR = CADTH Common Drug Review; CM = chronic migraine; ED = extendedly dominated; MOA = mode of administration; ICUR = incremental cost-utility ratio; Ona A = onabotulinum toxin A; QALY = quality-adjusted life-year.

[a] Results presented from the sponsor's base case were weighted, with 68% of the population having CM and 32% of the population having EM. Results from CADTH reanalyses assume a 100% CM population.

The following scenario analyses were conducted to explore sources of additional uncertainty.

Scenario analysis 1: Explore the effect of treatment waning. Given the CADTH clinical review team's assessment of the high levels of uncertainty in the efficacy results of the OLE studies of erenumab, reviewers explored the effect of treatment waning on CUA results by creating a scenario in which the effects of all treatments are reduced linearly over the model time horizon (five years) to eventually equal the baseline frequency of MMDs. 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 erenumab.

Scenario analysis 2 and 3: Use 10- and 20-year time horizons. The sponsor's submission included a five-year time horizon. In the sponsor's base case, at the end of five years, patients remained on all treatments. CADTH guidelines recommend using a time horizon that captures all costs and benefits from the intervention.[9] Extrapolating the time horizon adds uncertainty, given uncertain evidence on the long-term treatment efficacy of erenumab. As a result, 10- and 20-year time horizons are explored as scenario analyses only.

Scenario analysis 4: Use the sponsor's MMD distributions to calculate health-state utilities. Scenario 4 presents the CADTH base case without the inclusion of step 3 of the reanalysis.

Scenario analysis 5: Make the probability of response for Ona A equal to that of erenumab 140 mg. In the model, the probability of response for Ona A is implemented as an odds ratio relative to that of erenumab 140 mg based on the findings of the sponsor's ITC. Given the CADTH clinical review team's assessment of the ITC, reviewers explored a scenario whereby the effect of Ona A is equal to that of erenumab 140 mg.

Scenario analyses 1, 2, 3, and 4 were run in the indication EM population (Table 16) and the reimbursement-request EM population (Table 18). All scenario analyses were run in the indication CM population (Table 17) and reimbursement-request CM population (Table 19). In all scenarios in all populations, erenumab 70 mg was either extendedly dominated or dominated. Implementing the treatment-waning scenario increased the ICUR from the CADTH reanalyses in all populations. Results were somewhat sensitive to the model time horizon. Using the sponsor's approach to calculating health-state utilities by using treatment-specific distributions of MMDs reduced the CADTH base-case ICUR in all populations. Model results were most sensitive in the CM population to the probability of response for Ona A being equal to that of erenumab 140 mg. In the base-case population, this scenario led to sequential ICURs of $29,159 and $3,121,182 per QALY for Ona A and erenumab 140 mg, respectively. In the CM reimbursement-request population, this scenario led to sequential ICURs of $16,046 for Ona A compared to BSC and $3,084,516 per QALY for erenumab 140 mg compared to Ona A. Given the limitations of the sponsor's ITC and the wide confidence interval for the odds ratio of the probability of response for Ona A relative to erenumab 140 mg from the ITC, it appears that the uncertainty in this parameter estimate generated high levels of variability in the model results.

Price-Reduction Analyses

Price-reduction analyses were run separately for all patient populations on the sponsor's submission and CADTH base case. Table 20 presents price-reduction analysis results for the indication EM population. In the indication EM population, a price reduction of 64% is required for erenumab 140 mg to be considered cost-effective at a WTP threshold of $50,000 per QALY. Table 21 presents price-reduction analysis results for the indication CM population, for which a price reduction of 22% is required for erenumab 140 mg to be considered cost-effective at a WTP threshold of $50,000 per QALY.

Table 22 presents price-reduction analysis results for the reimbursement-request EM population. In this population, a price reduction of 49% is required for erenumab 140 mg to be considered cost-effective at a WTP threshold of $50,000 per QALY. Table 23 presents price-reduction analysis results for the reimbursement request CM population. In the CADTH base case for the reimbursement-request CM population, there is a 61% probability that erenumab 140 mg is optimal at a WTP of $50,000 without price reductions.

Issues for Consideration

Novartis provides a patient support program that includes a nurse to provide initial training on self-administration of erenumab.[2]

Patient Input

Input was received from Migraine Canada on behalf of its organization and Migraine Quebec. Migraine Canada conducted an online survey that included patients with EM and CM. Most patients had tried prior preventive medications. Patients noted that migraine's interferences with their lives were a primary concern and that migraine can lead to anxiety and depression. They also noted that it can take more than a year for some patients to see a neurologist or headache specialist.

Patients stated that currently available preventive treatments are insufficient, noting a lack of a cure and a low expectation for treatment outcomes. Patients reported that a 50% reduction in migraine frequency and a reduction in the intensity should be an acceptable outcome, highlighting the importance of considering not just the frequency of MMDs but also the severity of migraine attacks experienced by patients in the pharmacoeconomic analysis. Side effects were a problem with current treatments, and these often led to discontinuation of preventive medications. Expectations for new treatments include a decrease in headache days, a reduction in the severity of migraine attacks, an improvement in quality of life, and reduced or minimal side effects. The impact of AEs due to erenumab and the effect of erenumab on migraine severity were not taken into account in the sponsor's submission.

Conclusions

In all populations for both the indication and reimbursement request, erenumab 70 mg was extendedly dominated and erenumab 140 mg was more costly and more effective than BSC in all reanalyses. For CM patients in the indicated population, the ICUR for erenumab 140 mg compared with BSC was $66,359 per QALY and $153,635 per QALY in the EM population. In the reimbursement-request population, erenumab 140 mg compared with BSC was associated with an ICUR of $39,840 in the CM population and $105,695 in the EM population.

For erenumab 140 mg to be considered cost-effective at a WTP threshold of $50,000 per QALY, price reductions of 64% and 22% would be required for EM and CM patients, respectively. In the reimbursement population, a 49% price reduction would be required for EM patients, while for CM patients there is a 55% probability that erenumab 140 mg is cost-effective at a WTP threshold of $50,000 per QALY (no price reduction needed in this population). In all CADTH reanalyses, erenumab 70 mg was never optimal.

Appendix 1: Cost Comparison

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 be devices or procedures. Costs are sponsor list prices, unless otherwise specified. Existing product listing agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

Table 8: CDR Cost Comparison Table for Prophylaxis of Migraine

Drug or comparator	Strength	Dosage form	Price ($)	Recommended dosage	Average daily drug cost ($)	Average annual drug cost ($)
Erenumab (Aimovig)	70 mg/mL 140 mg/mL	Autoinjector	532.0000[a]	70 mg or 140 mg subcutaneously monthly	17.48[b]	6,384
Comparators indicated for prophylaxis of migraine						
Flunarizine (generics)	5 mg	Caplet	0.7348	10 mg daily	1.47	537
Onabotulinum toxin A (Botox)[c]	50 units 100 units 200 units	Injection vial	178.5000 357.0000 714.0000	155 units to 195 units every 12 weeks	8.47[c]	2,856 to 3,570[d]
Pizotyline or pizotifen (Sandomigran)	0.5 mg 1 mg	Tablet	0.3972 0.7982	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	50 mg twice daily	0.97	166[e]

CDR = CADTH Common Drug Review.

All prices are from the Ontario Drug Benefit Formulary[16] (accessed June 2019) unless otherwise indicated and do not include dispensing fees. All recommended doses sourced from respective product monographs.

[a] Sponsor's submitted price.

[b] The daily cost is based on the following calculation (532.00 × 12 months)/365.25 days.

[c] Indicated for use in chronic migraine only.[28]

[d] The daily cost is based on the following calculation 714.00 × (52 weeks/12-weekly injections)/365.25 days. The annual cost range is based on four or five courses of injections in a year.

[e] Source: Alberta Health Interactive Drug Benefit List[29] (accessed June 2019).

[e] The annual drug cost assumed a daily dose of 25 mg in week 1, 25 mg twice daily in week 2, and 50 mg twice daily in weeks 3 and beyond.[20] Dose based on using 25 mg and 100 mg tablets, assuming tablets may be split.

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

Drug or 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	Caplet	0.2905	500 mg to 1,500 mg per day[a,b]	0.58 to 1.74	212 to 637
	250 mg/5 mL	Oral sol	0.0398		0.08 to 0.24	29 to 87
	500 mg	Enteric coated caplet	0.6356		0.64 to 1.91	232 to 696
Gabapentin[a] (generics)	100 mg 300 mg 400 mg	Caplet	0.0416 0.1012 0.1206	1,200 mg to 1,800 mg per day[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	Caplet	0.2397 0.2940 0.5455 0.8066 1.3438	25 mg to 100 mg per day[b]	0.29 to 1.09	107 to 398
Nortriptyline[a,b] (generic)	10 mg 25 mg	Caplet	0.0500[c] 0.1011[c]	20 mg to 150 mg per day[a,b]	0.10 to 0.61	37 to 222
Venlafaxine[a,b] (generics)	37.5 mg 75 mg 150 mg	ER caplet	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 to 150 mg per day[b]	0.18 to 0.33	67 to 122
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	SR 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[a,b]	0.20 to 0.41	74 to 149
Verapamil[a,b] (generics)	80 mg 120 mg	Tablet	0.2735 0.4250	240 mg to 320 mg per day	0.82 to 1.09	300 to 400

Drug or comparator	Strength	Dosage form	Price ($)	Recommended dosage	Average daily drug cost ($)	Average annual drug cost ($)
	120 mg 180 mg 240 mg	SR tablet	0.5078[d] 0.5204 0.5075	divided in two doses[a,b]	0.51 to 0.78[e]	185 to 285
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
Anti-manic and/or mood stabilizer						
Lithium carbonate[b] (generics)	150 mg 300 mg 600 mg	Caplet	0.0667 0.0657 0.1988[f]	300 mg three times daily[b]	0.20	72
Lithium carbonate[b] (Lithmax)	300 mg	SR tablet	0.2495		0.75	273

ER = extended release; SR = sustained release.

Note: All prices are from the Ontario Drug Benefit Formulary[16] (accessed June 2019) unless otherwise indicated and do not include dispensing fees.

[a] Source: 2012 Canadian Headache Society Guideline for Migraine Prophylaxis.[30]

[b] Source: CPhA Therapeutic Choices: Medications for Migraine Prophylaxis[31] (accessed June 7, 2019).

[c] IQVIA database[32] (accessed June 2019).

[d] Source: Saskatchewan Online Formulary Database[33] (accessed June 2019).

[e] The maximum daily cost is for the 320 mg per day dose. As combinations of existing SR formulations (120 mg, 180 mg, and 240 mg) do not add up to 320 mg dose, 240 mg SR tablet and 80 mg standard tablet was assumed.

[f] Source: Alberta Drug Benefit List[29] (accessed July 2019).

Appendix 2: Additional Information

Table 10: Submission Quality

	Yes/ good	Somewhat/ average	No/ poor
Are the methods and analysis clear and transparent?			X
Comments Reviewer to provide comments if checking "no"	There was a lack of transparency regarding how different trial data were pooled and how MSQ data were mapped to EQ-5D utility values.		
Was the material included (content) sufficient?			X
Comments Reviewer to provide comments if checking "poor"	Reviewers made several requests to the sponsor for additional information regarding the background on the weighting of erenumab 70 mg and 140 mg doses, the indirect treatment comparison that included erenumab 70 mg, clarification regarding the derivation of long-term negative discontinuation rates, data to support long-term efficacy claims, and explanation of approach to pooling trial efficacy data. Reviewers also requested a model that ran and presented sequential results for all comparators simultaneously.		
Was the submission well organized and was information easy to locate?			X
Comments Reviewer to provide comments if checking "poor"	Reviewers requested clarification regarding the trials included in pooled trial data, the average MSQ value per MMD across pooled studies, and the approach to pooling MSQ data. Additionally, sources and values of AE frequency data used to derive utility decrements for erenumab and Ona A were not provided. Adverse event discontinuation rates for Ona A were reported by the sponsor to be derived from the indirect comparison; however, AEs were not looked at in the indirect treatment comparison.		

AE = adverse event; EQ-5D = EuroQol 5-Dimensions; MMD = monthly migraine day; MSQ = Migraine-Specific Quality of Life Questionnaire; Ona A = onabotulinum toxin A.

Table 11: Authors' Information

Authors of the pharmacoeconomic evaluation submitted to CADTH Common Drug Review
☐ Adaptation of Global model/Canadian model done by the sponsor
☒ Adaptation of Global model/Canadian model done by a private consultant contracted by the sponsor
☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the sponsor
☐ Other (please specify)

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis			X

Appendix 3: Summary of Other Health Technology Assessment Reviews of Erenumab

A review of erenumab is currently in progress with National Institute for Health and Care Excellence.[34] Recommendations listed are from a non-final appraisal consultation document.[35]

Table 12: Other Health Technology Assessment Findings

	NICE (non-final decision)[35]	SMC (March 2019)[36]
Treatment	Erenumab 70 mg or 140 mg administered every 4 weeks, subcutaneously.	
Price	£386.50 per 70 mg or 140 mg dose[35] ($657.82; £1 = $1.7020, Bank of Canada exchange rate)[37]	£5,024 to £10,049 per year[36] ($8,843 to $17,688; £1 = $1.7602, Bank of Canada exchange rate)[38]
Similarities with CDR submission	Similar model conceptualization: • Model structure: hybrid model with decision tree for 12-week assessment period, classifying patients as responders or nonresponders, and Markov model for post-assessment with 12-week cycle lengths[39,36] • Erenumab vs. BSC in EM, vs. Ona A and BSC in CM[36,39] • Response ≥ 50% reduction in MMDs[39 36] • Resource use dependent on MMDs; resource-use costs for each health state based on a weighted average of costs per MMD frequency, dependent on how patients in that state are distributed across MMDs; no AE costs[39] • Treatment effect remained constant while on treatment[39] • Positive discontinuation considered in a scenario analysis[35]	
Differences with CDR submission	• Population: adults with ≥ 3 prior failed treatments[36,39] • Considered whole migraine population, and considered CM and EM populations separately[39,40] • Proportion with CM: 66%[39] • Time horizon: 10 years[36,39] • Assumed a 50:50 blended dose of erenumab 70 mg and erenumab 140 mg[36,39] • Used ARISE trial, Study 295, STRIVE to map MSQ to EQ-5D using Gillard algorithm[10,36,39] • No AE disutility applied[39]	
Sponsor's results	Sponsor base case, whole population (EM and CM): ICUR erenumab £22,309 ($37,970)[37] per QALY vs. BSC for the blended dose (50:50 split between 70 mg and 140 mg doses), with confidential price reduction; for the whole population using 140 mg dose, the ICUR was £19,472 ($33,141)[37] per QALY, compared to BSC, with confidential price reduction[39]	Sponsor base case, whole population (EM and CM): ICUR erenumab £22,455 ($39,525)[38] per QALY vs. BSC for the blended dose (50:50 split between 70 mg and 140 mg doses) and an ICUR of £19,835 ($34,914)[38] for 140 mg dose, with a confidential price reduction[36]
Issues noted by the review group	• A sequential rather than pairwise analysis should be provided • EM and CM should be considered separately to align with trials and ensure all with ≥ 4 MMDs covered • The two erenumab doses should be considered separately; no patient will receive a blended dose; and a decision is required regarding which dose to provide • 10-year time horizon arbitrary, not representative of lifetime • Natural disease progression not captured • Uncertain long-term efficacy • No robust evidence comparing erenumab with Ona A	• Post hoc analysis to inform proposed positioning (adults with who have failed ≥ 3 prior treatments) based on small numbers, has potential for bias • Uncertainty in the comparative efficacy between erenumab and Ona A • Nonresponding patients who continue BSC were assumed to maintain their improvement in MMD reduction achieved at 12 weeks until end of time horizon • Uncertain long-term efficacy

	NICE (non-final decision)[35]	SMC (March 2019)[36]
	• Evidence does not include all comparators • No evidence to support positive discontinuation scenario assumption that erenumab benefit maintained indefinitely after stopping treatment	
Results of reanalyses by the review group (if any)	Evidence review group's base case: erenumab 140 mg ICUR of £15,641 ($26,261)[37] per QALY compared to BSC in CM (erenumab 70 mg strictly dominated);[35,39] for EM, erenumab 70 mg ICUR of £10,207 ($17,372) compared to BSC[37] and erenumab 140 mg was dominated;[35,39] results based on lifetime time horizon, adjustment of triptan costs, changes to MMD distributions for negative discontinuers;[39] scenario in which treatment effect of erenumab wanes over 5 years increased ICURs[35,39]	Not applicable
Recommendation	Non-final recommendation: erenumab not recommended for preventing migraine in adults who have at least 4 migraine days per month[35]	Erenumab approved for CM with ≥ 3 prior preventive treatment failures; patient access scheme improves the cost-effectiveness of erenumab[36]

AE = adverse event; BSC = best supportive care; CDR = CADTH Common Drug Review; CM = chronic migraine; EM = episodic migraine; EQ-5D = EuroQol 5-Dimensions; ICUR = incremental cost-utility ratio; MMD = monthly migraine day; MSQ = Migraine-Specific Quality of Life Questionnaire; NICE = National Institute for Health and Care Excellence; Ona A = onabotulinum toxin A; QALY = quality-adjusted life-year; SMC = Scottish Medicines Consortium; vs. = versus.

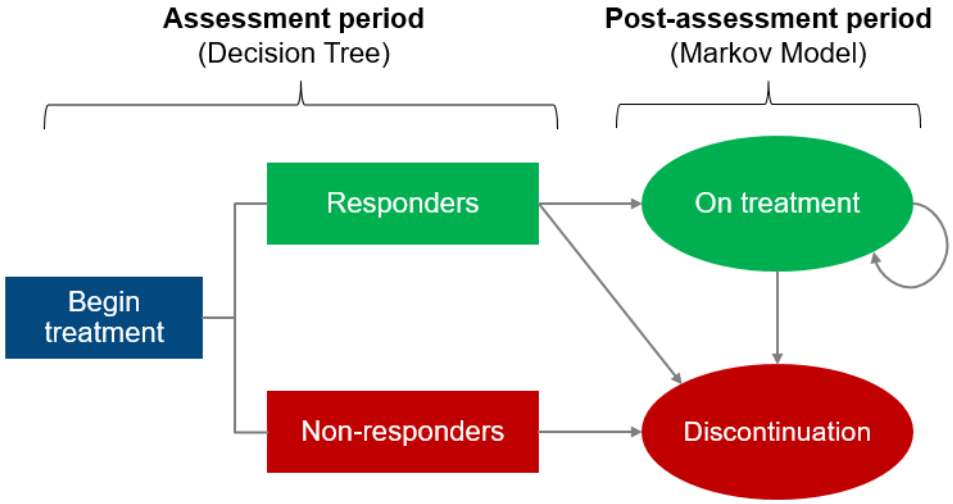
Appendix 4: Reviewer Worksheets

Sponsor's Model Structure

The sponsor used a decision-tree structure to represent a three-month assessment period and a Markov model to represent the post-assessment period.[2] A graphical representation of the model structure taken from the sponsor's submission is provided in Figure 1. The decision tree estimates the proportion of patients who are responders versus nonresponders to prophylactic treatment with erenumab versus BSC in the base case.[2] Comparison with Ona A for chronic migraine patients (those with at least eight MMDs) was considered in a scenario analysis.[2] Response to treatment was defined as a 50% reduction in MMDs between baseline and the end of the three-month assessment period.[2] Patients entered the model at 42 years of age, and were 82.8% female, based on baseline trial characteristics.[2]

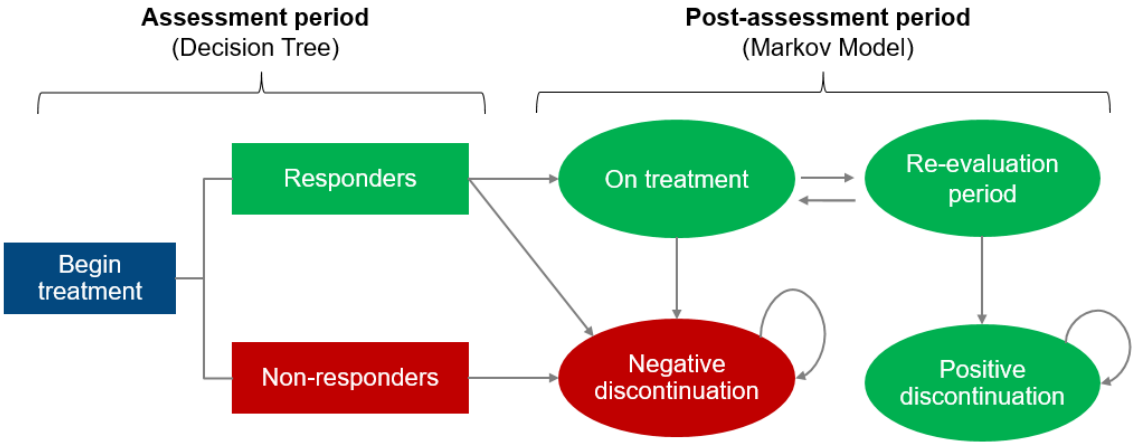
To assess the disease course in the post-assessment period, a Markov model structure with 12-week cycle lengths in which responders and nonresponders follow different treatment pathways was used. In the base case, responders may enter the "on treatment" health state or the "discontinuation" health state and nonresponders enter the discontinuation state.[2] In a scenario analysis, responders may also move from the "on-treatment" health state to a "re-evaluation period" health state.[2] From there, they may continue to be on treatment or enter a "positive discontinuation" state, in which patients who are having well-controlled migraine pause treatment and maintain treatment benefit for the duration of the model time horizon (Figure 2).[2] All patients have an equal probability of transitioning to a death state and there is no migraine-related mortality or differential mortality rates between treatment arms.[2] The model was conducted from a publicly funded health care payer perspective, adopted a five-year time horizon, and applied a half-cycle correction to health-state costs and QALYs.[2]

Figure 1: Model Structure for Sponsor's Base Case



Source: Sponsor's Pharmacoeconomic Submission.[2]

Figure 2: Model Structure with Re-Evaluation Period



Source: Sponsor's pharmacoeconomic submission.[2]

Table 13: Data Sources

Data input	Description of data source	Comment
Baseline characteristics	Age: 42 years[5] Proportion female: 82.8%[5]	Uncertain. According to the STRIVE CSR Table 9-3, 85.2% of patients were female and the average patient age was 40.9 years (SD of 11.2).[5] The baseline characteristics used in the model match those in Study 295.[4] Additionally, Study 295, STRIVE, and LIBERTY were used to inform efficacy outcomes, and justification as to why STRIVE was used to inform baseline characteristics was not provided. According to the sponsor, the baseline characteristics observed in STRIVE were similar to those observed in a Canadian study of migraine patients referred to by neurologists (average age of 39.7 years, 82.5% female).[11] According to the clinical expert consulted by CADTH for this review, the average age of patients in the studies is older than typical migraine patients seen in Canadian practices.
	Proportion of patients with CM for: • indication: 46%[11] • reimbursement request: 68% (estimated from midpoint of these studies)[12,27]	Inappropriate. The estimates used to define the proportion of CM patients in the model adds significant uncertainty to the model results. It would be more appropriate to consider these distinct populations, rather than a mixed population to assess the cost-effectiveness of erenumab in EM and CM patients.
Efficacy	The primary end point is the reduction in the frequency of MMDs, which are measured by the	Appropriate. Canadian Headache Society Guideline for Migraine Prophylaxis considers

Data input	Description of data source	Comment
	number of migraine days experienced by the patient in the previous 4 weeks.[2] Patients respond to treatment if they experience a reduction in MMDs of at least 50%.	prophylactic medication to be effective if migraine frequency is reduced by 50% or more.[30]
	Erenumab vs. BSC Study 295 was used to inform efficacy for CM population for the indication and reimbursement request.[4]	Appropriate
	Pooled dataset of STRIVE and LIBERTY was used to inform efficacy for EM for the indication and reimbursement request.[5,6]	Inappropriate. The sponsor's approach to pooling trial data was inappropriate, as it does not adjust for differences in baseline trial characteristics (see main text). Additionally, another trial in the EM population, ARISE, was not included on the basis that it was not a pivotal trial.[43] Given the similarity in study design among ARISE, Study 295, and STRIVE, excluding ARISE from the data pool appears to be inappropriate. If efficacy results from the ARISE trial are less promising, excluding this trial will overestimate the efficacy of erenumab and therefore favour erenumab. A more appropriate approach would be to conduct a meta-analysis of all trials in the EM population for both erenumab doses and BSC.
	Erenumab vs. Ona A An ITC was conducted comparing erenumab 140 mg versus Ona A in CM patients who had failed to respond to at least 3 previous treatments and who had not previously taken Ona A.[7] The ITC used data from Study 295 for erenumab and two pivotal trials for Ona A (PREEMPT 1 and PREEMPT 2).[4,41,42]	Inappropriate. The sponsor assumed that the results from a population that failed at least 3 previous treatments would not differ from those who had failed at least 2 previous treatments. This assumption was made as no data for Ona A in patients with at least two failures were available; however, this population is different from both the sponsor's indication and reimbursement request. The sponsor assumed that results obtained with treatment with erenumab 140 mg would be the same as those obtained with erenumab 70 mg, which will favour erenumab if the 140 mg dose is more effective in CM than erenumab 70 mg. Other methodological concerns noted in the key limitations section and the CADTH clinical report lead to uncertainty in the validity of the ITC.
	Long-term efficacy In the full post-assessment period, it was assumed that those who are on treatment maintain the improved frequency of MMDs achieved when response was established. Assumption supported by OLE Study 178.[14]	Uncertain. The sponsor provided data from an unpublished CSR of the ongoing OLE Study 178 to demonstrate the long-term efficacy of erenumab. However, according to the CADTH clinical review, there was uncertainty in the denominators used to

Data input	Description of data source	Comment
		calculate the proportion of responders, and lack of individual patient data regarding dose-switching adds uncertainty. The validity of the efficacy findings from Study 178 are highly uncertain.
	Discontinuation During the first 12-week cycle patients may discontinue erenumab due to AEs. Source: Study 295 and STRIVE for erenumab and BSC, ITC for Ona A.[4,5,7]	Inappropriate. Although the sponsor reports that the odds ratio for discontinuing Ona A relative to erenumab is sourced from the ITC, the ITC did not examine AE frequency or AE-related discontinuation.[7] The source of the OR for Ona A AE-related discontinuation therefore could not be validated by reviewers and is unclear. Additionally, the percentage of patients on erenumab or BSC discontinuing due to AEs does not change probabilistically in the model, whereas the percent of those on Ona A discontinuing treatment does change.
	In cycle 3 (after 36 weeks) 2.38% of all patients negatively discontinue, regardless of treatment. Source: all causes of discontinuation in the follow-up period of Study 178.[14]	Inappropriate. The sponsor's approach to calculating the discontinuation probability did not appropriately account for the exposure time when converting to per-cycle probabilities. Study 178 is an ongoing OLE. A recently published article by Ashina et al. (2019) provides more up-to-date data than what is provided in the CSR data cut-off used by the sponsor.[26] Given this input is used to model long-term discontinuation, it was considered more appropriate to use data that reflected the longest patient exposure to erenumab.
Natural history	The natural history of migraine was not incorporated in model.[2]	Uncertain. There is no natural change in disease severity incorporated in the analysis, which the sponsor notes is a simplifying assumption.[2] In reality, according to the clinical expert consulted by CADTH for this review, some patients will naturally recover or get worse. The impact of not including natural history in the model on the results of the analysis is unknown.
Utilities	To estimate health-state utilities, the sponsor established a mean utility value associated with each health state based on the distribution of patients across the number of MMDs in each health state.[2] MSQ data from Study 295 and STRIVE were mapped to EQ-5D utility values using an algorithm published by Gillard et al. (2012).[10] Using this data the sponsor conducted a multi-level regression model for predicting disutilities associated with MMDs to establish EQ-5D utility values as a function of MMDs.	Inappropriate. CADTH guidelines do not recommend using mapped utility values.[9] The mapping algorithm established by Gillard et al. (2012) used a UK value set; the utility values used in the model therefore do not reflect Canadian preferences.[10] The sponsor applied the EM or CM algorithm to patients using the definitions provided in the International Classification of Headache Disorders, third edition (i.e., EM patients have fewer than 15 monthly headache days and four to 14 MMDs, and CM patients have

Data input	Description of data source	Comment
		15 or more monthly headache days and eight or more MMDs) whereas Gillard et al. (2012) defined EM as fewer than 15 monthly headache days and CM as 15 or more monthly headache days.[10,25] MSQ data were also available in the ARISE trial, and excluding them from the pooled analysis was not justified.
	When applying utilities in the model, the sponsor multiplied the utility associated with the frequency of MMDs by the distributions of MMDs for each treatment at 12 weeks for responders and nonresponders, and at 24 weeks for those on treatment.	Inappropriate. Health states should capture all aspects of a disease and there should be no treatment-dependent differences between health states.
	MOA and AE utility decrements estimated from a UK vignette-based time trade-off utility-valuation study to estimate utilities associated with difference in treatment processes between erenumab and Ona A.[15] MOA-related decrement for OnaA: −0.060 AE-related decrement for OnaA: −0.001 AE-related decrement for BSC: 0.003 There was no MOA or AE decrement for erenumab.[2]	Uncertain. TTO study sponsored by sponsor.[15] As noted in CADTH's clinical review, AE rates were similar across erenumab 70 mg, erenumab 140 mg, and placebo in STRIVE. In Study 295, there were slightly lower percentages of people with AEs in the placebo group compared to the erenumab 70 mg and erenumab 140 mg groups. According to the clinical expert consulted by CADTH for this review, the MOA associated with Ona A elicits minimal discomfort in relation to that experienced by CM patients. MOAs and AEs were implemented in the model as utility decrements relative to erenumab; therefore, no decrement was associated with erenumab, and there was a positive decrement associated with BSC due to fewer AEs. A more plausible approach would have been to apply the utility decrements directly to the treatments.
AEs	The frequency of AEs used to calculate utility decrements in the model are sourced from Study 295 for erenumab and BSC and Dodick et al. (2010) for Ona A.[4,41] The AEs considered for erenumab and BSC were injection-site pain, pruritis, fatigue, insomnia, paranesthesia, and constipation. The AEs considered for Ona A were injection-site pain, neck stiffness, and pain and muscle weakness.	Inappropriate. AEs for erenumab should have been considered across all available trials, including trials for EM. Additionally, some AE frequencies were misreported from the CSR for Study 295. Given how AEs were relative to erenumab in the model, this is unlikely to affect model results.
Mortality	General population mortality sourced from Canadian life tables for the years 2013 to 2015 were used to estimate mortality.[44] No excess mortality associated with migraine was assumed.[2]	Appropriate. According to the clinical expert consulted by CADTH for this review, migraine patients have an increased risk of stroke, which may be associated with mortality, compared to the general population, although there was uncertainty

Data input	Description of data source	Comment
		regarding whether this risk would be a function of MMDs. If patients have an increased mortality risk with higher MMDs, assuming all patients have the same mortality risk is a conservative assumption.
Resource use and costs		
Drug costs	Price of erenumab submitted by the sponsor.[2] Price of Ona A sourced from the Ontario Drug Benefit formulary.[16] *Triptan costs* A linear regression was used to predict the number of migraine days with and without migraine-specific treatment per month as a function of MMDs.[2] Average cost per day for triptan medications was calculated by taking the cost of all triptans publicly dispensed in Ontario in the last three-quarters from the IMS PharmaStat database, then summing the costs and units of each triptan medication over each quarter to obtain total costs and units for each triptan. A weighted cost per unit was calculated for each medication to calculate the weighted mean triptan cost. The model assumes only one unit would be taken for each day that a triptan medication would be used.[2] *Other analgesics costs* Medications included were based on Canadian Headache Society guidelines.[45] Costs sourced from the Ontario Drug Benefit formulary.[16]	Appropriate Appropriate Appropriate
Administration costs	Assumed to be zero for erenumab and Ona A.[2]	Appropriate. Erenumab is assumed to be self-administered by the patient. Additionally, Novartis provides a patient support program that includes initial patient training for self-administration, such that they can self-administer at home.[2] Coverage of Ona A administration varies across the country and costs are currently only covered in Alberta.[2] Administration costs are reportedly paid by patients out of pocket.[2] Not including administration costs for Ona A is conservative in appraising erenumab's cost-effectiveness.
Resource-use costs	Hospitalization: OCCI CMG code 041 and all migraine diagnosis codes (G430, 431, 433, 438, 439) for patients aged 18-69, 2016-17.[46] Emergency room visit: OCCI CACS grouper B103 and all migraine codes (see above) for patients aged 18-59, 2016-17.[46] General practitioner visit: OSB code A005 (Consultation)[47]	Appropriate costing sources.

Data input	Description of data source	Comment
	Nurse visit: Statistics Canada Table 14-10-0306-01 Average hourly nursing wage in Canada in 2018.[48] Neurologist follow-up visit: Average of OSB codes A188, A184 and A181, based on sponsor's clinical expert.[47]	Inappropriate. Appropriateness of nurse visit is unclear. According to the clinical expert consulted by CADTH for this review, migraine patients would not have nurse visits. In addition, the sponsor notes that they provide a patient support program, which includes a nurse to provide initial training on how to administer the injection.[2]
	Frequency of occurrence of these events informed by a global online study sponsored by the sponsor, using resource utilization rates for Canadian participants experiencing 4 to 7, 8 to 14 and ≥ 15 MMDs.[17] Because the survey only included participants with at least 4 MMDs, for those experiencing 0 and 1 to 3 MMDs, resource utilization was informed by the Canadian results of the International Burden of Migraine Study.[13]	Inappropriate. The study by Martelletti (2018) used to populate visit frequency for patients with more than 4 MMDs was sponsored by Novartis.[17] The clinical expert consulted by CADTH for this review, expected a lower frequency of hospitalization days than used in the model, and a higher frequency of emergency room visits.
	Health-state costs are applied in the model based on the weighted average of the cost per MMD depending on how patients in each health state are distributed across MMDs.	Appropriate
AEs	Not included in base case.	Inappropriate. The sponsor assumed that the costs of AEs were too small to warrant inclusion in the analysis. AE costs could have been included for completeness; however, this is unlikely to influence model results.

AE = adverse event; BSC = best supportive care; CACS = Comprehensive Ambulatory Care Classification System; CM = chronic migraine; CMG = case mix group; CSR = Clinical Study Report; EM = episodic migraine; EQ-5D = EuroQol 5-Dimensions; ITC = indirect treatment comparison; MOA = mode of administration; MMD = monthly migraine day; MSQ = Migraine-Specific Quality of Life Questionnaire; OCCI = Ontario Case Costing Initiative; OLE = open-label extension; Ona A = onabotulinum toxin A; OSB = Ontario Schedule of Benefits; SD = standard deviation; TTO = time trade-off; vs. = versus.

Table 14: Sponsor's Key Assumptions

Assumption	Comment
Patients on treatment maintain the reduction in MMD achieved in the assessment period (i.e., no gain or loss in future treatment effects) over the full time horizon.[2]	Uncertain. The CADTH clinical review notes that the ability to draw conclusions regarding sustained erenumab efficacy is limited due to the lack of a control group and the inclusion of a protocol amendment, which saw doses switched from erenumab 70 mg to erenumab 140 mg where possible. A lack of patient-level data about the changes to dosing introduces uncertainty in the long-term results. Additionally, efficacy end points in Study 178 were exploratory and did not include statistical testing, making it difficult to interpret results. Overall, the interpretation of long-term efficacy results from Study 178 is significantly limited.
Treatment response defined as a 50% reduction in MMDs from the baseline to the end of the assessment period.[2]	Appropriate. This definition of treatment response is what is recommended in the Canadian Headache Society Guideline for Migraine Prophylaxis.[30]
Costs of AEs are too small to warrant inclusion.[2]	AE costs could have been included for completeness; however, this is unlikely to influence model results.

Assumption	Comment
Patients do not naturally change disease severity (i.e., no patients naturally improve or decline).[2]	Inappropriate. According to the clinical expert consulted by CADTH for this review, some patients may show a natural improvement or worsening in the frequency of migraines over time, regardless of treatment. The effect of this assumption on the model results is unknown.
Placebo is also a treatment to reduce migraine frequency. BSC patients who respond will continue to benefit.[2]	Placebo effects observed in trials were not removed during assessment and post-assessment period. This is a conservative assumption.
Patients who negatively discontinue treatment rebound to their baseline MMD frequency.[2]	Appropriate.
Patients who positively discontinue treatment are assumed to maintain the frequency of MMDs experienced by those on treatment.[2]	Inappropriate. There is no evidence to support that patients no longer receiving treatment will experience the same frequency of MMDs as those receiving treatment. As such, the scenario exploring positive discontinuation was not explored by CADTH reviewers.
The effect of erenumab 140 mg is assumed to be the same as the 70 mg dose in the indirect treatment comparison.[2]	Inappropriate. There is evidence to suggest different treatment effects between erenumab doses. If erenumab 140 mg is more effective than erenumab 70 mg, this will favour erenumab.

AE = adverse event; BSC = best supportive care; MMD = monthly migraine day; Ona A = onabotulinum toxin A.

Sponsor's Results

Table 15: Summary of Results of the Sponsor's Scenario, Comparison with Onabotulinum Toxin A in Chronic Migraine Subgroup

	Total costs ($)	Total QALYs	Incremental cost ($) vs. BSC	Incremental QALYs vs. BSC	Incremental cost ($) per QALY, vs. BSC	Sequential ICUR ($ per QALY)
BSC	13,083	2.54				
Ona A	15,769	2.56	2,686	0.02	131,540	ED
Erenumab 70 mg	22,038	2.75	8,955	0.21	42,974	ED
Erenumab 140 mg	23,163	2.86	10,080	0.32	31,414	31,414

BSC = best supportive care; ED = extendedly dominated; ICUR = incremental cost-utility ratio; Ona A = onabotulinum toxin A; QALY = quality-adjusted life-year.

Source: Results from sponsor's updated pharmacoeconomic model.[8]

CADTH Common Drug Review Reanalyses

Results of CADTH Common Drug Review Scenario Analyses

Table 16: CDR Scenario Analyses in the Indication, Episodic Migraine Population

	Scenario	Treatment	QALYs	Cost ($)	Sequential ICUR ($ per QALY)
	CADTH base case, indication, EM	BSC	3.32	5,424	
		erenumab 70 mg	3.39	15,620	ED
		erenumab 140 mg	3.39	16,112	153,635
S1	**Treatment-waning in the indication, EM population**	BSC	3.30	5,570	
		erenumab 70 mg	3.35	15,842	ED
		erenumab 140 mg	3.35	16,344	193,736

	Scenario	Treatment	QALYs	Cost ($)	Sequential ICUR ($ per QALY)
S2	10-year time horizon in the indication, EM population	BSC	6.49	10,295	
		erenumab 70 mg	6.59	25,933	ED
		erenumab 140 mg	6.60	26,717	146,352
S3	20-year time horizon in the indication, EM population	BSC	11.88	20,452	
		erenumab 70 mg	12.00	39,104	ED
		erenumab 140 mg	12.01	40,097	145,115
S4	Using sponsor's treatment distributions for calculating health-state utilities in the indication, EM	BSC	3.31	5,428	
		erenumab 70 mg	3.39	15,596	ED
		erenumab 140 mg	3.39	16,106	135,024

BSC = best supportive care; CDR = CADTH Common Drug Review; ED = extendedly dominated; EM = episodic migraine; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Table 17: CDR Scenario Analyses in the Indication, Chronic Migraine Population

	Scenario	Treatment	QALYs	Cost ($)	Sequential ICUR ($ per QALY)
	CADTH base case, indication, CM population	BSC	2.66	9,577	
		Ona A	2.64	12,739	Dominated
		erenumab 70 mg	2.80	19,418	ED
		erenumab 140 mg	2.81	19,621	66,359
S1	Treatment waning in the indication, CM population	BSC	2.59	9,938	
		Ona A	2.57	13,090	Dominated
		erenumab 70 mg	2.68	20,038	ED
		erenumab 140 mg	2.70	20,271	94,437
S2	10-year time horizon in the indication, CM population	BSC	5.13	19,349	
		Ona A	5.10	23,883	Dominated
		erenumab 70 mg	5.34	33,823	ED
		erenumab 140 mg	5.36	34,134	63,391
S3	20-year time horizon in the indication, CM population	BSC	9.27	36,643	
		Ona A	9.23	42,205	Dominated
		erenumab 70 mg	9.54	54,651	ED
		erenumab 140 mg	9.56	55,043	62,467
S4	Using sponsor's treatment distributions for calculating health-state utilities in the indication, CM	BSC	2.65	9,570	
		Ona A	2.63	12,730	Dominated
		erenumab 70 mg	2.79	19,404	ED
		erenumab 140 mg	2.81	19,601	62,150
S5	Probability of response for Ona A equal to erenumab 140 mg in the indication, CM population	BSC	2.66	9,574	
		Ona A	2.81	13,891	29,159
		erenumab 70 mg	2.80	19,421	Dominated

	Scenario	Treatment	QALYs	Cost ($)	Sequential ICUR ($ per QALY)
		erenumab 140 mg	2.81	19,593	3,121,182

BSC = best supportive care; CDR = CADTH Common Drug Review; CM = chronic migraine; ED = extendedly dominated; ICUR = incremental cost-utility ratio; Ona A = onabotulinum toxin A; QALY = quality-adjusted life-year.

Table 18: CDR Scenario Analyses in the Reimbursement Request, Episodic Migraine Population

	Scenario	Treatment	QALYs	Cost ($)	Sequential ICUR ($ per QALY)
	CADTH base case, reimbursement request, EM	BSC	3.21	6,123	
		erenumab 70 mg	3.26	13,602	ED
		erenumab 140 mg	3.29	14,762	105,695
S1	**Treatment waning in the reimbursement request, EM population**	BSC	3.19	6,183	
		erenumab 70 mg	3.22	13,697	ED
		erenumab 140 mg	3.25	14,963	133,995
S2	**10-year time horizon in the reimbursement request, EM population**	BSC	6.28	12,142	
		erenumab 70 mg	6.37	23,016	ED
		erenumab 140 mg	6.41	24,763	100,812
S3	**20-year time horizon in the reimbursement request, EM population**	BSC	11.51	22,523	
		erenumab 70 mg	11.62	35,858	ED
		erenumab 140 mg	11.67	38,105	98,256
S4	**Using sponsor's treatment distributions for calculating health-state utilities in the reimbursement request, EM**	BSC	3.20	6,096	
		erenumab 70 mg	3.23	13,597	ED
		erenumab 140 mg	3.29	14,740	94,049

BSC = best supportive care; CDR = CADTH Common Drug Review; ED = extendedly dominated; EM = episodic migraine; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Table 19: CDR Scenario Analyses in the Reimbursement Request, Chronic Migraine Population

	Scenario	Treatment	QALYs	Cost ($)	Sequential ICUR ($ per QALY)
	CADTH base case, reimbursement request, CM population	BSC	2.54	10,314	
		Ona A	2.60	12,847	ED
		erenumab 70 mg	2.73	18,762	ED
		erenumab 140 mg	2.78	19,511	39,840
S1	**Treatment waning in the reimbursement request, CM population**	BSC	2.51	10,474	
		Ona A	2.55	13,170	ED
		erenumab 70 mg	2.63	19,244	ED
		erenumab 140 mg	2.67	20,156	58,942
S2	**10-year time horizon in the reimbursement request, CM population**	BSC	4.93	20,577	
		Ona A	5.02	24,133	ED
		erenumab 70 mg	5.22	32,895	ED
		erenumab 140 mg	5.29	34,117	37,650
S3	**20-year time horizon in the reimbursement request, CM population**	BSC	8.98	38,534	
		Ona A	9.10	42,851	ED
		erenumab 70 mg	9.35	53,779	ED
		erenumab 140 mg	9.43	55,269	37,269
S4	**Using sponsor's treatment distributions for calculating health-state utilities in the reimbursement request, CM**	BSC	2.53	10,307	
		Ona A	2.60	12,839	36,067
		erenumab 70 mg	2.71	18,757	ED
		erenumab 140 mg	2.77	19,526	38,736
S5	**Probability of response for Ona A equal to erenumab 140 mg in the reimbursement request, CM population**	BSC	2.54	10,300	
		Ona A	2.77	13,972	16,046
		erenumab 70 mg	2.73	18,785	Dominated
		erenumab 140 mg	2.77	19,526	3,084,516

BSC = best supportive care; CM = chronic migraine; CDR = CADTH Common Drug Review; ED = extendedly dominated; ICUR = incremental cost-utility ratio; Ona A = Onabotulinum toxin A; QALY = quality-adjusted life-year.

Results of Price-Reduction Analyses

Table 20: CDR Reanalysis Price Reduction in the Indication, Episodic Migraine Population

ICURs of erenumab versus comparators		
Price	**Base-case analysis submitted by sponsor**	**Reanalysis by CADTH**
Submitted	If λ < $84,204 BSC is optimal If λ ≥ $84,204 erenumab 140 mg is optimal	If λ < $153,635 BSC is optimal If λ ≥ $153,635 erenumab 140 mg is optimal
10% reduction	If λ < $117,451 BSC is optimal If $117,451 > λ < $118,791 erenumab 70 mg is optimal If λ ≥ $118,791 erenumab 140 mg is optimal	If λ < $136,093 BSC is optimal If λ ≥ $136,093 erenumab 140 mg is optimal
30% reduction	If λ < $88,666 BSC is optimal If λ ≥ $88,666 erenumab 140 mg is optimal	If λ < $103,954 BSC is optimal If λ ≥ $103,954 erenumab 140 mg is optimal
50% reduction	If λ < $60,904 BSC is optimal If $60,904 > λ < $64,126 erenumab 70 mg is optimal If λ ≥ $64,126 erenumab 140 mg is optimal	If λ < $71,963 BSC is optimal If λ ≥ $71,963 erenumab 140 mg is optimal
60% reduction	If λ < $46,831 BSC is optimal If $46,831 > λ < $47,696 erenumab 70 mg is optimal If λ ≥ $47,696 erenumab 140 mg is optimal	If λ < $56,189 BSC is optimal If λ ≥ $56,189 erenumab 140 mg is optimal
65% reduction	If λ < $40,018 BSC If λ ≥ $40,018 erenumab 140 mg	If λ < $47,965 BSC is optimal If λ ≥ $47,965 erenumab 140 mg is optimal
70% reduction	If λ < $32,835 BSC is optimal If $32,835 > λ < $33,511 erenumab 70 mg is optimal If λ ≥ $33,511 erenumab 140 mg is optimal	If λ < $40,042 BSC is optimal If λ ≥ $40,042 erenumab 140 mg is optimal
75% reduction	If λ < $25,834 BSC If λ ≥ $25,834 erenumab 140 mg	If λ < $31,637 BSC is optimal If λ ≥ $31,637 erenumab 140 mg is optimal
80% reduction	If λ < $18,911 BSC is optimal If $18,911 > λ < $20,357 erenumab 70 mg is optimal If λ ≥ $20,357 erenumab 140 mg is optimal	If λ < $23,814 BSC is optimal If λ ≥ $23,184 erenumab 140 mg is optimal

λ = willingness-to-pay threshold; BSC = best supportive care; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio.

Table 21: CDR Reanalysis Price Reduction in the Indication, Chronic Migraine Population

ICURs of erenumab versus comparators		
Price	**Base-case analysis submitted by sponsor**	**Reanalysis by CADTH**
Submitted	If λ < $84,204 BSC is optimal If λ ≥ $84,204 erenumab 140 mg is optimal	If λ < $66,359 BSC is optimal If λ ≥ $66,359 erenumab 140 mg is optimal
10% reduction	If λ < $53,729 BSC is optimal If λ ≥ $53,729 erenumab 140 mg is optimal	If λ < $59,013 BSC is optimal If λ ≥ $59,013 erenumab 140 mg is optimal
15% reduction	If λ < $50,111 BSC is optimal If λ ≥ $50,111 erenumab 140 mg is optimal	If λ < $55,440 BSC is optimal If λ ≥ $55,440 erenumab 140 mg is optimal
20% reduction	If λ < $46,721 BSC is optimal If λ ≥ $46,721 erenumab 140 mg is optimal	If λ < $51,417 BSC is optimal If λ ≥ $51,417 erenumab 140 mg is optimal
25% reduction	If λ < $43,298 BSC is optimal If λ ≥ $43,298 erenumab 140 mg is optimal	If λ < $48,110 BSC is optimal If λ ≥ $48,110 erenumab 140 mg is optimal
30% reduction	If λ < $40,149 BSC is optimal If λ ≥ $40,149 erenumab 140 mg is optimal	If λ < $44,050 BSC is optimal If λ ≥ $44,050 erenumab 140 mg is optimal
50% reduction	If λ < $26,106 BSC is optimal If λ ≥ $26,106 erenumab 140 mg is optimal	If λ < $29,473 BSC is optimal If λ ≥ $29,473 erenumab 140 mg is optimal

ICURs of erenumab versus comparators		
Price	**Base-case analysis submitted by sponsor**	**Reanalysis by CADTH**
60% reduction	If λ < $19,491 BSC is optimal If λ ≥ $19,491 erenumab 140 mg is optimal	If λ < $22,335 BSC is optimal If λ ≥ $22,335 erenumab 140 mg is optimal

λ = willingness-to-pay threshold; BSC = best supportive care; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio.

Table 22: CDR Reanalysis Price Reduction in the Reimbursement Request, Episodic Migraine Population

ICURs of erenumab versus comparators		
Price	**Base-case analysis submitted by sponsor**	**Reanalysis by CADTH**
Submitted	If λ < $46,704 BSC is optimal If λ ≥ $46,704 erenumab 140 mg is optimal	If λ < $105,695 BSC is optimal If λ ≥ $105,695 erenumab 140 mg is optimal
10% reduction	If λ < $82,415 BSC is optimal If λ ≥ $82,415 erenumab 140 mg is optimal	If λ < $94,421 BSC is optimal If λ ≥ $94,421 erenumab 140 mg is optimal
30% reduction	If λ < $62,008 BSC is optimal If λ ≥ $62,008 erenumab 140 mg is optimal	If λ < $71,595 BSC is optimal If λ ≥ $71,595 erenumab 140 mg is optimal
40% reduction	If λ < $51,944 BSC is optimal If λ ≥ $51,944 erenumab 140 mg is optimal	If λ < $59,515 BSC is optimal If λ ≥ $59,515 erenumab 140 mg is optimal
45% reduction	If λ < $46,574 BSC is optimal If λ ≥ $46,574 erenumab 140 mg is optimal	If λ < $54,545 BSC is optimal If λ ≥ $54,545 erenumab 140 mg is optimal
50% reduction	If λ < $42,086 BSC is optimal If λ ≥ $42,086 erenumab 140 mg is optimal	If λ < $48,855 BSC is optimal If λ ≥ $48,855 erenumab 140 mg is optimal
70% reduction	If λ < $21,630 BSC is optimal If λ ≥ $21,630 erenumab 140 mg is optimal	If λ < $26,193 BSC is optimal If λ ≥ $26,193 erenumab 140 mg is optimal
75% reduction	If λ < $16,730 BSC is optimal If λ ≥ $16,730 erenumab 140 mg is optimal	If λ < $20,664 BSC is optimal If λ ≥ $20,664 erenumab 140 mg is optimal

λ = willingness-to-pay threshold; BSC = best supportive care; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio.

Table 23: CDR Reanalysis Price Reduction in the Reimbursement Request, Chronic Migraine Population

ICURs of erenumab versus comparators		
Price	**Base-case analysis submitted by sponsor**	**Reanalysis by CADTH**
Submitted	If λ < $46,704 BSC is optimal If λ ≥ $46,704 erenumab 140 mg is optimal	If λ < $39,840 BSC is optimal If λ ≥ $39,840 erenumab 140 mg is optimal
10% reduction	If λ < $31,759 BSC is optimal If λ ≥ $31,759 erenumab 140 mg is optimal	If λ < $35,075 BSC is optimal If λ ≥ $35,075 erenumab 140 mg is optimal
20% reduction	If λ < $27,211 BSC is optimal If λ ≥ $27,211 erenumab 140 mg is optimal	If λ < $30,591 BSC is optimal If λ ≥ $30,591 erenumab 140 mg is optimal
25% reduction	If λ < $25,235 BSC is optimal If λ ≥ $25,235 erenumab 140 mg is optimal	If λ < $28,284 BSC is optimal If λ ≥ $28,284 erenumab 140 mg is optimal
30% reduction	If λ < $22,905 BSC is optimal If λ ≥ $22,905 erenumab 140 mg is optimal	If λ < $25,879 BSC is optimal If λ ≥ $25,879 erenumab 140 mg is optimal
40% reduction	If λ < $18,557 BSC is optimal If λ ≥ $18,557 erenumab 140 mg is optimal	If λ < $21,051 BSC is optimal If λ ≥ $21,051 erenumab 140 mg is optimal

λ = willingness-to-pay threshold; BSC = best supportive care; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio.

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