CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

OnabotulinumtoxinA (Botox)

(Allergan Inc.)

Indication: For the prophylaxis of headaches in adults with chronic migraine (≥ 15 days per month with headache lasting four hours a day or longer)

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CADTH

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

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Abbreviations

BSC	best supportive care
CM	chronic migraine
ED	emergency department
EM	episodic migraine
EQ-5D	EuroQol 5-Dimensions questionnaire
HDPM	headache days per month
HIT-6	six-item Headache Impact Test
IBMS	International Burden of Migraines Study
ICUR	incremental cost-utility ratio
IPD	individual patient data
ITT	intention-to-treat
MSQ	Migraine-Specific Quality of Life Questionnaire
Ona A	onabotulinumtoxinA
QALY	quality-adjusted life-year
U	Allergan units
WTP	willingness to pay

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	OnabotulinumtoxinA (Ona A; Botox) for injection
Study Question	Is Ona A cost-effective as a prophylactic treatment option for patients with chronic migraine (CM), compared with existing treatments?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adult patients in Canada with CM, defined as ≥ 15 headache days per month (28 days) with headaches lasting four hours a day or longer
Treatment	OnabotulinumtoxinA 155 U to 195 U
Outcome	Quality-adjusted life-years (QALYs)
Comparators	Best supportive care (BSC) Topiramate was considered in scenario analysis
Perspective	Canadian public health care payer
Time Horizon	Three years (5, 10, and 30 years in scenario analyses)
Results for Base Case	ICUR = $34,407 per QALY gained for Ona A vs. BSC. At a willingness to pay of $50,000 Ona A was found to have a 64% probability of being the optimal intervention.
Key Limitations	• The manufacturer's model structure, using HDPM-based health states, did not explicitly consider headache severity and may not appropriately capture clinically meaningful changes in the condition. The manufacturer also assumed patients who improved from CM to EM continued treatment, which may not be aligned with current clinical practice in Canada. • The comparative clinical evidence for Ona A was associated with uncertainty. BSC was approximated using evidence based on the placebo arms of the PREEMPT studies, and the relationship between placebo and BSC is unclear. BSC as defined in the model may not be representative of BSC in Canadian practice. The CADTH Clinical Review identified substantial limitations with the FORWARD study, which compared Ona A with topiramate, thus the cost-effectiveness estimate of Ona A compared with topiramate is uncertain. • Extrapolation of transition probabilities based on short-term data allowed perpetual clinical improvement or worsening in contrast to clinical feedback, which suggests the health state is maintained.
CDR Estimates	• CADTH could not address several key limitations, including the model structure and quality of the comparative clinical evidence. Cost-effectiveness of Ona A for the prophylaxis of CM remains uncertain. • CADTH undertook reanalyses using revised baseline characteristics, utilities, adverse events, long-term transition probabilities, and cost inputs. • In the CADTH base case, the ICUR was $134,601 per QALY gained for Ona A vs. BSC. At a willingness to pay of $50,000 per QALY, Ona A was associated with a 9% probability of being the optimal intervention. A price reduction of more than 75% is required to achieve an ICUR of less than $50,000 per QALY. • CADTH also conducted reanalyses on the manufacturer's scenario analysis comparing Ona A vs. topiramate, resulting in an estimated ICUR of $28,968 per QALY. However, this result is uncertain given the limitations with the comparative study data.

BSC = best supportive care; CDR = CADTH Common Drug Review; CM = chronic migraine; EM = episodic migraine; HDPM = headache days per month; ICUR = incremental cost-utility ratio; Ona A = onabotulinumtoxinA; QALY = quality-adjusted life-year.

Drug	OnabotulinumtoxinA (Botox)
Indication	For the prophylaxis of headaches in adults with chronic migraine (≥ 15 days per month with headache lasting four hours a day or longer),
Reimbursement Request	As per indication
Dosage Forms	Sterile vacuum-dried concentrate powder for solution for injection; 50, 100, and 200 Allergan units per vial
NOC Date	October 18, 2011
Manufacturer	Allergan, Inc.

NOC = Notice of Compliance.

Executive Summary

Background

OnabotulinumtoxinA (Ona A; Botox) powder for intramuscular injection solution is a neuromuscular paralytic agent derived from the fermentation of *Clostridium botulinum* type A and is one of several immunologically distinct serotypes of botulinum neurotoxin.[1] It is indicated for the prophylaxis of headaches in adults with chronic migraine (CM) who have headaches that occur at least 15 days per month and last four hours a day or longer. Ona A is administered as a minimum of 31 injections and a maximum of 39 injections of five Allergan units (U) per injection to the head and neck (total: 155 U to 195 U per administration). The recommended retreatment schedule is every 12 weeks.[2] Ona A is available in 50 U, 100 U, and 200 U vial sizes, at a cost of $178.50, $357.00, and $714.00 per vial, respectively ($3.57 per U). CADTH Canadian Drug Expert Committee previously reviewed Ona A in 2014 for CM and provided a do-not-list recommendation due to significant limitations of the underlying clinical evidence.[3]

The manufacturer submitted a cost-utility analysis for this resubmission that was similar to the initial submission in 2014.[4] In the current submission, the manufacturer compared Ona A with best supportive care (BSC) for the prophylaxis of headaches in adults with CM over a three-year time horizon. The manufacturer also compared Ona A with topiramate in a pairwise scenario analysis to account for changes in clinical practice since the original submission. The Markov model in the resubmission attempted to address some of the previous limitations identified by CADTH by considering additional health care resource use and costs, and added health states to model headache frequency changes in patients who discontinue treatment. The manufacturer modelled 13 health states: six headache frequency health states (0 to 3, 4 to 9, 10 to 14, 15 to 19, 20 to 23, and 24 to 28 headache days per month [HDPM]) for each treatment status (i.e., on treatment or discontinued treatment due to treatment failure) and a death state. Patients entered the model in the various health states based on headache frequency distribution from a pooled analysis of the PREEMPT trials, and transitioned between states every 12 weeks. Similar to the original submission, efficacy and discontinuation data from the PREEMPT trials were pooled and used to inform transition probability for Ona A and BSC; placebo was used as a proxy for BSC. The manufacturer modelled response-based discontinuation based on current clinical practice, in which patients who do not experience a reduction of at least 50% in headache frequency

after the initial 24 weeks discontinue treatment. Patients discontinuing Ona A or BSC were assumed to be treated with BSC (patients treated with BSC effectively did not discontinue).

The manufacturer reported that Ona A was associated with an additional cost of $3,430 and generated an additional 0.10 quality-adjusted life-years (QALYs) compared with BSC, resulting in an incremental cost-utility ratio (ICUR) of $34,407 per QALY. At a willingness-to-pay threshold of $50,000 per QALY, the manufacturer reported that Ona A was associated with a 64% probability of being the optimal intervention compared with BSC.

Summary of Identified Limitations and Key Results

Despite the revisions to the manufacturer's model to address limitations identified in the 2014 review of Ona A, CADTH identified several key limitations with the manufacturer's economic evaluation, some which remained from the original submission.

The three key limitations were associated with the model structure and assumptions regarding the clinical pathway, the uncertainty associated with the comparative effectiveness data, and the extrapolation of short-term data over a longer time horizon.

First, it was uncertain whether the manufacturer's model structure sufficiently captured a spectrum of health states that are meaningful to patients with CM, as the headache frequency–based health states used by the manufacturer do not appropriately account for other important aspects of CM, such as headache severity, and the existing literature on these health states was not informative as to whether they are clinically distinct. Although the manufacturer attempted to consider other aspects of CM using treatment-specific health-state utilities, this does not adhere to best practices for economic modelling. The manufacturer's assumption that patients who improved from CM to episodic migraine (EM) would continue to receive Ona A does not align with current public insurance coverage in Ontario, which indicates that patients should not continue to receive Ona A after improving to EM.[5] As practice may differ across jurisdictions in Canada, it is uncertain how EM is managed in Canada in patients who previously had CM.

Second, the comparative clinical evidence for Ona A was associated with uncertainty. The placebo injection arm from the PREEMPT trials was used to approximate BSC for the manufacturer's base-case analysis. However, the validity of this assumption is uncertain as it is unclear what treatments constitute BSC in Canada. The manufacturer used data from the FORWARD trial for the scenario analysis comparison of Ona A with topiramate. The CADTH Clinical Review highlighted several methodological limitations that could have biased the results in favour of Ona A. As such, the incorporation of these data indicates that the cost-effectiveness estimates for Ona A compared with BSC and topiramate are uncertain. Furthermore, the manufacturer did not support its use of subgroup-based transition probabilities with clear clinical evidence, contributing further uncertainty to the treatment impact in the model.

Third, the use of short-term data to inform change in headache frequency was extrapolated over the time horizon, allowing perpetual improvement or worsening. According to the clinical expert consulted by CADTH, once patients are on treatment beyond a year, those who do not respond would not receive further treatment and that patients were unlikely to improve or worsen, indicating a maintenance of effect over time. The clinical expert indicated that in Canadian practice, patients have received Ona A for CM for up to 10 years.

Additional limitations were identified, including application of treatment-specific baseline patient characteristics, inappropriate sourcing and application of adverse event data, a failure to consider drug wastage, outdated emergency department visit costs, and the use of pairwise comparison when a sequential analysis that assessed Ona A with all relevant comparators (BSC, topiramate, and erenumab) should have been explored.

CADTH undertook reanalyses of the manufacturer's model to address the above limitations where possible. CADTH could not address limitations associated with the model structure and the quality of the comparative evidence. In the CADTH base case, Ona A is associated with an ICUR of $134,601 per QALY compared with BSC. At a willingness to pay $50,000 per QALY, Ona A was associated with a 9% probability of being the optimal intervention. When comparing Ona A with topiramate, Ona A was associated with an ICUR of $28,968 per QALY; however, concerns with the available comparative efficacy information require that these results be viewed with caution.

Conclusions

CADTH identified several key limitations with the manufacturer's model. Based on a series of reanalyses, CADTH estimated that the ICUR of Ona A compared with BSC was $134,601 per QALY. At a willingness to pay $50,000 per QALY, Ona A was associated with a 9% probability of being the optimal intervention compared with BSC. A price reduction of more than 75% is required for Ona A to achieve an ICUR of less than $50,000 per QALY compared with BSC.

However, given the limitations with the model structure and comparative effectiveness data that could not be adequately addressed in CADTH reanalyses, the cost-effectiveness of Ona A for the prophylaxis of CM remains uncertain.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Resubmission

The manufacturer submitted a new cost-utility analysis as part of its resubmission to CADTH, which compared onabotulinumtoxinA (Ona A) injections with best supportive care (BSC; assumed by the manufacturer as an unspecified group of acute-pain medications) for prophylaxis of headaches in adults with chronic migraine (CM). CM is defined as at least 15 days per month with headache lasting at least four hours a day or longer.[6] A scenario analysis comparing Ona A with topiramate was also presented by the manufacturer to account for a change in clinical practice since the original submission. Both analyses assumed concurrent use of acute-headache medications, including triptans, based on headache frequency. The cost-utility analysis was conducted as a Markov cohort-state transition model from the perspective of a Canadian publicly funded health care payer and utilized a three-year time horizon with 12-week cycles.

The manufacturer modelled six headache frequency health states (0 to 3, 4 to 9, 10 to 14, 15 to 19, 20 to 23, and 24 to 28 headache days per month [HDPM]) for each treatment status (i.e., on treatment or discontinued treatment due to treatment failure) and a death state (13 total health states). Six of the health states reflected HDPM observed in CM (i.e., 15 to 19, 20 to 23, and 24 to 28 health states) and six others reflected HDPM observed in episodic migraine (EM) (i.e., 0 to 3, 4 to 9, and 10 to 14 health states). The baseline characteristics of the modelled population, treatment efficacy, and discontinuation differed by treatment and were based on pooled data from two trials within the manufacturer's PREEMPT trial program, which compared Ona A injections with placebo injections. The placebo injection arm was used to inform BSC in the model. Patients enter the model in one of the six health states (predominantly in one of the three CM health states) and could transition to other headache frequency health states every 12 weeks. The transition probabilities were informed by individual patient data (IPD) from the PREEMPT trials populations and subgroups based on treatment response (using the "stopping rules" defined later) and prior treatment failure.[6] The model was structured so that patients with the same headache frequency could be assigned two different health-state utilities depending on whether they received Ona A or BSC or discontinued treatment. These utility values were mapped from Migraine-Specific Quality of Life Questionnaire (MSQ) results from the PREEMPT trials.

Patients discontinuing Ona A or BSC were assumed to be treated with BSC (patients treated with BSC effectively did not discontinue). A "stopping rule" based on treatment response was applied such that those who do not experience a reduction of at least 50% in headache frequency after two cycles of treatment (24 weeks) discontinued treatment (red arrows in Figure 1), reflecting current clinical guideline[7] and reimbursement criteria.[5] The manufacturer also incorporated scenarios with other "stopping rules": less than 30% reduction in headache frequency within the first 24 weeks, and patients who achieved zero to three HDPM. In the latter scenario, patients who achieved zero to three HDPM were also assumed to discontinue treatment independently of the < 50% HDPM reduction treatment-discontinuation rule. These patients were assumed to restart treatment when headache frequency increased to at least 15 HDPM again for more than 12 weeks (i.e., one cycle).

Patients could also transition to the death state based on the mortality risk of the general Canadian population.

Health care resource utilization (i.e., physician consultation, neurologist consultation, emergency department [ED] visit, hospitalization, and triptan treatment) was assumed to differ by whether patients had EM (fewer than 14 headaches per month) or CM (at least 15 headaches per month), based on the rates observed in the International Burden of Migraine Study (IBMS).[8] Treatment-emergent adverse events that occurred in more than 2% of patients in the PREEMPT trials were modelled (i.e., neck pain, muscular weakness, musculoskeletal stiffness, myalgia, and eyelid ptosis). These adverse events were not assumed to affect health utilities in the base-case analysis, but half of the adverse events were assumed to result in a physician visit. Direct medical costs were included in the model. Drug acquisition, administration, and monitoring costs for the comparator treatments were included. Generally, unit costs from Ontario Case Costing Initiative, Ontario schedule of benefits, and Canadian Institute for Health Information were incorporated. The cost of Ona A administration was based on the Alberta Health Care Insurance Plan, and the cost of triptan treatment was based on IQVIA PharmaStat private claims data.[6]

The manufacturer's resubmission incorporated revisions to account for several limitations identified in the original submission of Ona A for CM. Additional "discontinue treatment" health states in the new pharmacoeconomic model allowed the resubmission to be more transparent about patients who discontinue treatment. The manufacturer's scenario analyses of longer time horizons, < 30% headache frequency reduction stopping rule, and discontinuation of some patients with improved headache symptoms were aimed at addressing concerns regarding these aspects identified in CADTH's appraisal of the previous submission.

Manufacturer's Base Case

The base case results are presented in Table 2. Compared with BSC, Ona A accrued 0.10 incremental QALYs at an additional cost of $3,430, with an incremental cost-utility ratio (ICUR) $34,407 per additional QALY. The manufacturer reported that Ona A had a 64% probability of being cost-effective at a willingness-to-pay (WTP) threshold of $50,000 per QALY, and a 77% probability of being cost-effective at a WTP threshold of $100,000 per QALY.

Table 2: Summary of Results of the Manufacturer's Base Case

Comparator	Total Cost ($)	Incremental Cost vs. BSC ($)	Total QALYs	Incremental QALYs vs. BSC	Incremental Cost per QALY ($) vs. BSC
BSC	3,584	-	1.77	-	-
OnabotulinumtoxinA	7,014	3,430	1.87	0.10	34,407

BSC = best supportive care; QALY = quality-adjusted life-year.

Source: Manufacturer's pharmacoeconomic submission.[6]

Summary of Manufacturer's Key Scenario Analysis

As part of the resubmission, the manufacturer presented new evidence, in the form of a scenario analysis in which Ona A was compared with topiramate. This analysis was based on inputs derived from the FORWARD trial, a 36-week randomized open-label trial that compared Ona A (155 Allergan units) and topiramate (25 mg daily, titrated up to 100 mg

daily). Transition probabilities for the Ona A and topiramate arm of the scenario analysis were derived from IPD from the corresponding arms of the FORWARD trial. As the trial did not have a BSC arm, patients who discontinued treatment in the scenario analysis were assumed to follow the same transition probabilities of the patients who discontinued treatment in the base-case analysis, which were informed by IPD from the placebo injection arm of the PREEMPT trials. The health utilities in the model were treatment-independent and derived from the IBMS.[6] Treatment-emergent adverse events that occurred in more than 2% of patients in the FORWARD trial were modelled. As in the manufacturer's base case, these events were not assumed to affect health utilities and half of the events were assumed to result in a physician visit.[6] The manufacturer reported that compared with topiramate, Ona A was associated with an ICUR of $13,283 per QALY. As no information on the total costs for each treatment was provided, CADTH replicated the manufacturer's analysis to derive the results presented in Table 3.

Table 3: Summary of Results of the Manufacturer's Base Case

Comparator	Total Cost ($)	Incremental Cost vs. Topiramate ($)	Total QALYs	Incremental QALYs vs. Topiramate	Incremental Cost per QALY ($) vs. Topiramate
Topiramate	3,943	-	1.35	-	-
OnabotulinumtoxinA	7,283	3,339	1.60	0.25	13,283

QALY = quality-adjusted life-year.

Source: Derived from the manufacturer's pharmacoeconomic submission.[6]

Summary of Manufacturer's Additional Analyses

The manufacturer also conducted a number of additional scenario analyses (Table 14). The pharmacoeconomic model was most sensitive to a change in perspective (to societal), time horizon, different target population, treatment stopping rule, consideration of drug wastage, and the use of treatment-independent health utilities. The alternate assumptions using a societal perspective, longer time horizon, target population with prior oral prophylaxis treatment failures, and treatment discontinuation response criteria of less than 30% reduction in headache frequency all resulted in a reduced ICUR (range: $24,000 per QALY to $31,000 per QALY). Having no response-based rules, including drug wastage, and using treatment-independent health-state utility values resulted in an increased ICUR (range: $40,000 per QALY to $45,000 per QALY).

The results of the manufacturer's topiramate comparison scenario analysis were relatively stable in two additional analyses of different discontinuation rates (Table 14).

Limitations of Manufacturer's Submission

CADTH identified the following key limitations in the resubmission:

- **It is uncertain whether the model structure sufficiently captures a spectrum of health states that are meaningful to patients with chronic migraine:** Results from the IBMS, which reported EuroQol 5-Dimensions questionnaire (EQ-5D) utility values for the same health states (defined by headache frequency) used by the manufacturer, are not informative as to whether the health states defined by the manufacturer are clinically distinct.[9] The HDPM ranges assigned to each health state were not based on clinical evidence that showed meaningful quality-of-life differences, but were instead

inappropriately based in part on baseline HDPM distribution from PREEMPT trials.[6] The same study showed that there is a statistically significant difference in utility values between patients with EM (< 15 HDPM) and patients with CM (≥ 15 HDPM),[9] indicating that reducing health states to these two conditions may better reflect the meaningful difference in quality of life. As noted in the CADTH Clinical Review report, there is uncertainty around the absolute numerical difference between groups of approximately one to two headache and migraine days reported in PREEMPT-1 and PREEMPT-2 in the original CADTH Common Drug Review, and whether they are clinically meaningful.

As the manufacturer acknowledged in its resubmission, a model structure based on headache frequency does not capture other clinically meaningful aspects of CM, such as headache severity.[6] The clinical expert consulted by CADTH indicated that the relationship between headache frequency and severity was not linear (i.e., patients who have fewer headaches could have fewer or more severe headaches). Thus, the manufacturer's model may overestimate the impact of a change in HDPM in patient quality of life. The manufacturer assigned treatment-dependent health-state utility values to patients experiencing the same headache frequency in an attempt to incorporate headache severity and duration into the model. The use of treatment-specific utilities is not recommended by CADTH,[10] and headache severity and duration should have been incorporated in the model in a treatment-independent manner.

Overall, the model structure based on treatment-specific headache frequency health states has limited face validity. The direction and the magnitude of impact on the model's cost-effectiveness results are unclear.

- **Clinical management of patients with episodic migraine is uncertain:** The manufacturer assumes that patients who initially have CM (i.e., ≥ 15 HDPM) and improve to EM (i.e., < 15 HDPM) continue to receive treatment in the model, which does not reflect existing Ona A public drug insurance coverage in Ontario.[5] Feedback from the clinical expert consulted by CADTH indicated that a potential treatment-and-relapse cycle may arise when patients are forced to discontinue and are allowed to restart treatment only after relapsing back into CM. The health-state transition probabilities used in the manufacturer's base case assigned higher probabilities of transitioning to EM states to Ona A-treated patients than to BSC-treated patients, which resulted in patients on Ona A accruing more QALY benefit than patients on BSC. However, it is uncertain whether such stopping criteria would be enacted across all Canadian jurisdictions, which may affect the overall cost-effectiveness estimates.
- **Key comparators were not comprehensively incorporated in the base case**: The manufacturer's base-case analysis presented a comparison between Ona A and BSC. According to the clinical expert consulted by CADTH, topiramate and erenumab are considered to be key comparators for prophylactic therapy in patients with CM in Canada. Although the manufacturer conducted a scenario analysis that compared Ona A with topiramate, an analysis of all comparators simultaneously allowing for a sequential analysis would have been the preferred approach for the base case.
- **Uncertain comparative clinical evidence between Ona A and key comparators**: According to the clinical expert consulted by CADTH, it is uncertain what combination of therapies would constitute BSC in Canada. A number of migraine prophylaxis treatments are available (Table 7 and Table 8). The data used to inform BSC in the model was from the placebo injection arm from the PREEMPT trials. It is unclear whether the efficacy and safety profile of placebo injection is similar to BSC as assumed by the manufacturer. Furthermore, the manufacturer incorporated transition probabilities based on subgroups of patients with different numbers of prior prophylactic treatment failures or different

response-based stopping rules (i.e., discontinue if < 30% or < 50% headache frequency reduction in 24 weeks). CADTH clinical reviewers could not identify evidence regarding statistically significant differences in efficacy based on these subgroups, and it is unclear whether clinically meaningful differences exist between these subgroups.

The FORWARD trial was used to inform the manufacturer's scenario analysis comparison of Ona A and topiramate. CADTH clinical reviewers determined the comparative evidence from this trial was uncertain due to a number of limitations, including the open-label trial design, and high discontinuation rate in the topiramate arm compared with the Ona A arm. Data from a published indirect treatment comparison indicated that, based on a Bayesian network meta-analysis, Ona A was not favoured over topiramate or calcitonin gene-related peptide inhibitors in terms of change from baseline in monthly migraine days, change from baseline in monthly headache days, and all-cause discontinuation. CADTH clinical reviewers considered these results to be limited by heterogeneity that was not systematically evaluated and generalizability to the patient population of interest.

- **Extrapolation of short-term data is uncertain**: The transition probabilities for week 24 to year 3 (approximately 132 weeks) of the model were informed by short-term data for Ona A (32-week period from PREEMPT trials) and BSC patients (12-week period from PREEMPT trials) data. These transition probabilities allow perpetual improvement and worsening of headache frequency, which may not reflect clinical observations. The clinical expert consulted by CADTH provided feedback that patients who continue to receive treatment for CM would experience a plateau in their reduction in HDPM and maintenance of headache frequency.
- **Inclusion of adverse-event data in the model is associated with uncertainty**: The manufacturer modelled adverse events based on the percentages reported between week 24 and 36 of the PREEMPT trial. Given that evidence for the first 24 weeks is available, CADTH considered that incorporating the totality of evidence would have been preferred. As this period was the start of the open-label phase of the trial, the adverse events do not reflect a difference between Ona A and placebo safety profiles that is controlled by double-blinding. Additionally, the manufacturer also did not use an appropriate methodology[11] to transform probabilities based on the length of the trial (24 weeks for PREEMPT, 36 weeks for FORWARD) to the model's cycle length of 12 weeks.

  The manufacturer also incorporated an arbitrary health disutility of 0.05 for each of the adverse events in a number of scenario analyses. It is uncertain how this arbitrary value relates to the true utility decrement associated with the adverse events. Furthermore, the disutility calculation in the model was not tied to proportion of treated or live patients, reducing the validity of these scenario analyses.
- **Patient characteristics were assumed to differ between treatment groups at baseline**: Patients entered the model health states in different proportions based on whether the patients received Ona A or BSC. Patients who received BSC were assumed to have lower overall headache frequency than those who received Ona A at baseline. While this may better approximate the baseline characteristics of PREEMPT, it is unlikely to be reflective of clinical practice, and any differences in model results between treatment groups should be solely due to different efficacy and harm profiles of the treatments that are explicitly reflected in the model structure. [redacted]
- **Inappropriate cost assumptions and inputs**: The manufacturer did not consider drug wastage and used the 2009 unit cost for ED visits. Incorporating drug wastage and using

more recent ED visit costs would better reflect the current costs to the health care system, although the proportions of patients requiring an ED visit for CM remain uncertain.

Furthermore, CADTH reviewers identified that the model does not consider adverse-event costs in patients who discontinue initial treatment. It is uncertain how accounting for these adverse events would further change cost differences between the compared treatments.

CADTH Common Drug Review Reanalyses

CADTH could not address model limitations associated with the lack of comprehensive consideration of key comparators, uncertain comparative evidence, and the clinical management of patients with EM.

Other limitations were addressed as possible:

1. Alternate treatment-independent utility values directly based on, instead of derived from, IBMS:
   (a) by HDPM health states, based on IBMS survey respondents who completed EQ-5D and HIT-6.
   (b) by HDPM health states, based on IBMS survey respondents who completed EQ-5D and MSQ.
   (c) by CM and EM health states, based on IBMS survey respondents.
2. Alternate adverse-event probabilities based on the 24-week double-blind period of PREEMPT trials, converted to 12-week cycle probabilities using Fleurence and Hollenbeak's methodology.11
3. Same age, sex, and headache frequency baseline characteristics assumed for all treatment groups based on both arms of PREEMPT trials, no patients below 15 HDPM at baseline.
4. Alternate transition probabilities:
   (a) transition probabilities of patients who discontinued treatment based on intention-to-treat (ITT) population.
   (b) long-term treatment transition probabilities (beyond 24 weeks) based on ITT population.
   (c) transition probabilities based on 4a and 4b.
5. Long-term plateauing and maintenance of headache frequency reduction efficacy.
6. Updated ED cost and drug-wastage consideration.

In the CADTH base case, consisting of: 1c, 2, 3, 4c, 5, and 6, Ona A produced an additional 0.03 QALYs at an incremental cost of $4,168 compared with BSC, resulting in an ICUR of $134,601 per QALY (Table 4). At a willingness to pay of $50,000 per QALY, Ona A was associated with a 9% probability of being the optimal intervention compared with BSC.

CADTH conducted additional scenario analyses exploring the use alternate utilities, treatment stopping rule, time horizon, costs, and long-term transition probabilities (Table 17). The CADTH base case was found to be relatively robust in the majority of the scenarios explored. A longer time horizon of 10 years reduced the ICUR to $73,092 per QALY.

Table 4: CADTH Reanalysis (OnabotulinumtoxinA vs. Best Supportive Care)

	Analysis	Comparator	Cost ($)	QALYs	ICUR ($ per QALY Gained)
	Manufacturer's base case	Ona A	7,014	1.87	-
		BSC	3,584	1.77	-
		Incremental	*3,430*	*0.10*	*34,407*
1a	IBMS utility based on EQ-5D and HIT-6 survey responders	Ona A	7,012	1.71	-
		BSC	3,582	1.64	-
		Incremental	*3,431*	*0.08*	*45,246*
1b	IBMS utility based on EQ-5D and MSQ survey responders	Ona A	7,012	1.74	-
		BSC	3,579	1.66	-
		Incremental	*3,432*	*0.08*	*43,049*
1c	**IBMS utility (CM vs. EM)**	**Ona A**	**7,012**	**1.80**	**-**
		BSC	**3,581**	**1.74**	**-**
		Incremental	***3,431***	***0.05***	***63,225***
2	**Updated adverse events**	**Ona A**	**7,028**	**1.87**	**-**
		BSC	**3,587**	**1.77**	**-**
		Incremental	***3,441***	***0.10***	***33,952***
3	**Updated baseline characteristics**	**Ona A**	**7,020**	**1.87**	**-**
		BSC	**3,590**	**1.77**	**-**
		Incremental	***3,430***	***0.10***	***33,650***
4a	Post-treatment discontinuation transition probabilities based on ITT	Ona A	7,026	1.86	-
		BSC	3,576	1.77	-
		Incremental	*3,450*	*0.09*	*39,174*
4b	Transition probabilities beyond 24 weeks based on ITT	Ona A	6,887	1.88	-
		BSC	3,444	1.78	-
		Incremental	*3,443*	*0.10*	*35,234*
4c	**4a and 4b**	**Ona A**	**6,905**	**1.87**	**-**
		BSC	**3,445**	**1.78**	**-**
		Incremental	***3,461***	***0.09***	***38,882***
5	**Long-term efficacy plateau and maintenance**	**Ona A**	**6,922**	**1.86**	**-**
		BSC	**3,304**	**1.79**	**-**
		Incremental	***3,617***	***0.07***	***51,748***
6	**Updated ED cost and drug wastage**	**Ona A**	**7,876**	**1.87**	**-**
		BSC	**3,852**	**1.77**	**-**
		Incremental	***4,024***	***0.10***	***40,385***
CADTH base case					
B1	1c, 2, 3, 4c, 5, & 6	Ona A	8,085	1.76	-
		BSC	3,917	1.73	-
		Incremental	*4,168*	*0.03*	*134,601*

BSC = best supportive care; CM = chronic migraine; ED = emergency department; EQ-5D = EuroQol 5-Dimensions questionnaire; EM = episodic migraine; HDPM = headache days per month; HIT-6 = six-item Headache Impact Test; IBMS = International Burden of Migraine Study; ICUR = incremental cost-utility ratio; ITT= intention-to-treat; MSQ = Migraine-Specific Quality of Life Questionnaire; Ona A = onabotulinumtoxinA; QALY = quality-adjusted life-year.

As topiramate was considered a relevant comparator, a similar set of reanalyses was also applied to the manufacturer's scenario analysis comparison of Ona A and topiramate (Table 5), altered to accommodate two different adverse-event reanalyses:

1. Alternate treatment-independent utility values based on IBMS:
   (a) by HDPM health states, based on IBMS survey respondents who completed EQ-5D and HIT-6
   (b) by HDPM health states, based on IBMS survey respondents who completed EQ-5D and MSQ
   (c) by CM and EM health states, based on IBMS survey respondents
2. Alternate adverse-event data:
   (a) alternate adverse-event probabilities based on the 36-week FORWARD trial period, converted to 12-week cycle probabilities using Fleurence and Hollenbeak's methodology[11]
   (b) corrected adverse-event disutility calculation, adverse-event rates are based on proportion of on-treatment patients rather than on proportion of patients that enter the model
3. Same age, sex, and headache frequency baseline characteristics assumed for all treatment groups based on both arms of PREEMPT trials, with no patients below 15 HDPM at baseline
4. Alternate transition probabilities:
   (a) transition probabilities of patients who discontinued treatment based on ITT population
   (b) long-term treatment transition probabilities (beyond 24 weeks) based on ITT population
   (c) transition probabilities based on 4a and 4b
5. Long-term plateauing and maintenance of headache frequency reduction efficacy
6. Updated ED cost and drug-wastage consideration.

CADTH scenario analysis of the Ona A and topiramate comparison consisted of reanalyses 1c, 2a, 3, 4c, 5, and 6, and did not incorporate the arbitrary 0.05 disutility that the manufacturer used in the manufacturer's scenario analysis. Ona A produced an additional 0.13 QALY at an incremental cost of $3,648 compared with topiramate, resulting in an ICUR of $28,968 per QALY (Table 5). At a WTP threshold of $50,000 per QALY, Ona A was associated with an 85.5% probability of being the optimal intervention compared with topiramate. The same set of additional scenario analyses were conducted for the CADTH scenario analysis of comparison of Ona A and topiramate (Table 19). CADTH could not address the substantial limitations with regards to the comparative effectiveness of Ona A and topiramate identified by the clinical reviewers, and as such, the results should be viewed with caution.

Table 5: CADTH Reanalysis (OnabotulinumtoxinA vs. Topiramate)

	Analysis	Comparator	Cost ($)	QALYs	ICUR ($ per QALY Gained)
	Manufacturer's scenario analysis	Ona A	7,283	1.60	-
		Topiramate	3,493	1.35	-
		Incremental	*3,339*	*0.25*	*13,283*
CADTH topiramate comparison scenario analyses					
T1	1c, 2a, 3, 4c, 5, 6, and no adverse-event disutilities*	Ona A	7,799	1.86	-
		Topiramate	4,151	1.74	-
		Incremental	*3,648*	*0.13*	*28,968*

CM = chronic migraine; ED = emergency department; EQ-5D = EuroQol 5-Dimensions questionnaire; EM = episodic migraine; HDPM = headache days per month; HIT-6 = six-item Headache Impact Test; ICUR = incremental cost-utility ratio; ITT= intention-to-treat; MSQ = Migraine-Specific Quality of Life Questionnaire; Ona A = onabotulinumtoxinA; QALY = quality-adjusted life-year.

*See Table 18 for the results of the reanalyses that were incorporated.

Table 6: CADTH Price Reduction Scenarios

ICURs of Ona A versus BSC		
Price	**Base-case analysis submitted by manufacturer**	**Reanalysis by CADTH**
Submitted	$34,407 per QALY	$134,601 per QALY
20% reduction	$28,370 per QALY	$111,175 per QALY
40% reduction	$23,258 per QALY	$89,735 per QALY
60% reduction	$17,178 per QALY	$67,545 per QALY
75% reduction	$12,922 per QALY	$50,433 per QALY
76% reduction	$12,815 per QALY	$48,591 per QALY
80% reduction	$11,377 per QALY	$45,425 per QALY

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

Issues for Consideration

- Feedback from the clinical expert consulted by CADTH suggested that in clinical practice, a 30% reduction in headache frequency may be considered an appropriate response. This differs from the current clinical criteria in Ontario[5] and the current treatment guidelines (which focus on EM),[7] which recommend a reduction of at least 50% in headache frequency after 24 weeks. Furthermore, based on the criteria observed in Ontario, patients are required to stop receiving treatment three months after achieving < 15 HDPM (EM).[5] However, patients often relapse after discontinuing treatment due to achieving EM parameters and will have to start treatment again when headache frequency increases to CM levels (≥ 15 HDPM).
- Based on the feedback from the clinical expert consulted by CADTH, the use of Ona A for prophylaxis of CM may extend outside of the Health Canada indication to continuing treatment for patients once they achieve EM.
- According to a clinical expert consulted by CADTH, Ona A administration cost may be borne by patients as an out-of-pocket cost because the procedure may not be covered by a public health insurance plan, as is the case in Ontario. CADTH reanalyses have explored this scenario.

- The burden of CM to the patients may extend beyond health implications to social considerations, including ability to work. The manufacturer has conducted a scenario analysis from a societal perspective that accounts for potential productivity loss.

Patient Input

Input was received from Migraine Canada, which partnered with Migraine Québec to undertake two online patient surveys that included CM patients. The patients reported that migraine is an important cause of visits to the ED, confirming the importance of capturing the impact of CM prophylaxis on this health care resource use as already done by the manufacturer. Patient inputs also considered Ona A to be a long-term therapy for CM, suggesting the importance of considering a longer time horizon. The majority of patients surveyed reported CM affected their professional life, although only 15% of participants reported being able to go back to work in some capacity after using Ona A. It is uncertain how this finding relates to the manufacturer's societal perspective scenario analysis, which captured productivity loss by headache frequency based on an American study.[6]

The patients reported that CM is associated with anxiety and depression, with 51% of patients reporting a moderate-to-severe effect of migraine on their mood. The impact of prophylactic treatments on these comorbid conditions is not explored in this review. Existing prophylactic therapies are also reported to be poorly tolerated, indicating a need to explore the impact of adverse events in the economic evaluation. The current review is not able to explore this consideration in detail. The patients also reported that, although Ona A may be used as a monotherapy for prevention, it may be combined with another preventive medication or multiple preventive medications. These reports point to a possible research gap that could be filled by additional pharmacoeconomic analyses involving comparisons of combination treatments and treatment sequences, pending available evidence in this treatment space.

Conclusions

CADTH identified several key limitations with the manufacturer's model. Based on a series of reanalyses, CADTH estimated that the ICUR of Ona A compared with BSC was $134,601 per QALY. At a WTP threshold of $50,000 per QALY, Ona A was associated with a 9% probability of being the optimal intervention compared with BSC. A price reduction of more than 75% is required for Ona A to achieve an ICUR of less than $50,000 per QALY compared with BSC.

However, given the limitations with the model structure and comparative effectiveness data that could not be adequately addressed in CADTH reanalyses, the cost-effectiveness of Ona A for the prophylaxis of CM remains uncertain.

Appendix 1: Cost Comparison

The comparators presented in Table 7 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 manufacturer 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 7: CADTH Cost Comparison Table for Prophylaxis of Chronic Migraine (Medications with Migraine Prophylaxis Indication)

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
OnabotulinumtoxinA (Botox)	50 U 100 U 200 U	Injection vial	178.5000 357.0000 714.0000	155 U to 195 U every 12 weeks[a]	8.47[b]	2,856 to 3,570[b]
Comparators indicated for prophylaxis of migraine						
Pizotyline/Pizotifen[c,d] (Sandomigran)	1.0 mg	Tablet	0.7735	1.5 mg to 4 mg per day[c,d] 1.5 mg to 6 mg per day[e]	1.16 to 3.09 1.16 to 4.64	424 to 1,130 424 to 1,695
Topiramate[c,d] (generics)	25 mg 100 mg 200 mg	Tablet	0.2433 0.4583 0.6748	50 mg to 200 mg per day[c,d] 50 mg twice per day[f]	0.49 to 0.67 0.97	178 to 246 355
Flunarizine[c,d] (generics)	5 mg	Capsule	0.7348	10 mg per day[c,d,g]	1.47	537
Erenumab	70 mg	Pre-filled syringe for injection	532.0000[h]	70 mg to 140 mg monthly[i]	17.48 to 34.96	6,384 to 12,768

U = Allergan units.

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

[a] Product monograph states that: "The use of one vial for more than one patient is not recommended because the product and diluent do not contain a preservative."[2] Thus, wastage has been included for onabotulinumtoxinA in this table.

[b] The daily cost is based on the following calculation (= [714.00 x (52 weeks/12-weekly injections)]/365.25 days). The annual cost range is based on 4 or 5 courses of injections in a year.

[c] Source: 2012 Canadian Headache Society Guideline for Migraine Prophylaxis.[7]

[d] Source: CPhA Therapeutic Choices: Medications for Migraine Prophylaxis[12] (accessed January 3, 2019).

[e] Source: Sandomigran product monograph.[13]

[f] Source: Apo-Topiramate product monograph.[14]

[g] Source: Flunarizine product monograph.[15]

[h] Wholesale acquisition price based on IQVIA DeltaPA database[16] (accessed January 3, 2019).

[i] Source: Aimovig product monograph.[17]

Table 8: CADTH Cost Comparison Table for Prophylaxis of Chronic Migraine (Off-Label Medications)

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Anti-epileptics						
Divalproex Sodium[a,b] (generics)	125 mg 250 mg 500 mg	Enteric 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
Gabapentin[a] (generics)	100 mg 300 mg 400 mg	Capsule	0.0416 0.1012 0.1206	1,200 mg to 1,800 mg per day[a]	0.36 to 0.56	132 to 206
Valproate[a,b] (generics)	250 mg / 5 mL	Oral solution	0.199	500 mg to 1,500 mg per day[a,b]	0.40 to 1.19	145 to 436
Antidepressants						
Amitriptyline[a,b] (Elavil)	10 mg 25 mg 50 mg	Tablet	0.0435 0.0829 0.1540	20 mg to 150 mg per day[a,b]	0.09 to 0.46	32 to 169
Doxepin[b] (generic)	10 mg 25 mg 50 mg 75 mg 100 mg	Capsule	0.2397 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] (generic)	10 mg 25 mg	Capsule	0.2570 0.5193	20 mg to 150 mg per day[b]	0.51 to 3.89	188 to 1,408
Venlafaxine[a,b] (generics)	37.5 mg 75 mg 150 mg	ER capsule	0.0913 0.1825 0.1927	150 mg per day[a,b]	0.19	70
Antihypertensives						
Atenolol[b] (generics)	50 mg 100 mg	Tablet	0.1107 0.1821	100 to 150 mg per day[b]	0.18 to 0.27	67 to 100
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 0.40	74 to 149
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
Metoprolol[a,b] (generics)	50 mg 100 mg	Tablet	0.0624 0.1361	100 mg to 200 mg per day[a,b]	0.14 to 0.27	50 to 99
	100 mg 200 mg	SR tablet	0.1415 0.2568		0.14 to 0.26	52 to 94
Verapamil[a,b] (generics)	80 mg 120 mg	Tablet	0.2735 0.4250	80 mg three to four times daily[a,b]	0.82 to 1.09	300 to 400
	120 mg 180 mg 240 mg	SR tablet	0.5078[c] 0.5204 0.5075	240 mg to 320 mg per day divided in two doses[a,b]	0.51 to 0.78[d]	185 to 285
Candesartan[a] (generics)	4 mg 8 mg 16 mg	Tablet	0.1700 0.2281 0.2281	16 mg per day[a]	0.28	83

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
	32 mg		0.2281			
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						
Lithium carbonate[b] (generics)	150 mg 300 mg	Capsule	0.0667 0.0657	300 mg three times daily[b]	0.20	72

ER = extended release; SR = sustained release.

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

[a] Source: 2012 Canadian Headache Society Guideline for Migraine Prophylaxis.[7]

[b] Source: CPhA Therapeutic Choices: Medications for Migraine Prophylaxis[12] (accessed January 3, 2019).

[c] Source: Saskatchewan Online Formulary Database[18] (February 2019).

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

Appendix 2: Additional Information

Table 9: Submission Quality

	Yes/Good	Somewhat/Average	No/Poor
Are the methods and analysis clear and transparent?			X
Comments	24-week adverse-event probabilities were reported to be extracted and converted to 12-week cycle probabilities. 12-week adverse-event probabilities based on week 24 to week 36 of the PREEMPT trials were instead extracted, and the conversion only occurred for adverse-event costs, not probabilities.		
Was the material included (content) sufficient?			X
Comments	Inappropriate adverse-event and cost sources were used. Adverse-event disutilities were inappropriately incorporated in scenario analyses.		
Was the submission well organized and was information easy to locate?		X	
Comments	None.		

Table 10: Authors' Information

Authors of the Pharmacoeconomic Evaluation Submitted to CADTH Common Drug Review
☐ Adaptation of Global model/Canadian model done by the manufacturer
☒ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer
☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer
☐ 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 Drug

In the previous CADTH Common Drug Review of onabotulinumtoxinA (Ona A) for the prophylaxis of chronic migraine in adults, CADTH had presented findings from the National Institute for Health and Care Excellence, Scottish Medicines Consortium, and Pharmaceutical Benefits Advisory Committee.[4] Since that time, the Scottish Medicines Consortium published a reconsideration of Ona A in 2017.[19] The findings are summarized in Table 11.

Table 11: Other Health Technology Assessment Findings

	SMC 2017[19]
Treatment	Onabotulinumtoxin A (Ona A), 50 units, 100 units, 200 units, powder for solution for injection.
Price	£1,380 per year (1.00 GBP = 1.63 CAD; January 2017)[20]
Similarities with CDR submission	• CUA comparing Ona A vs. BSC, using a Markov model structure with on-treatment and off-treatment health states based on mean HDPM. 12-week cycle length and 3-year time horizon. • BSC assumed to be as effective as placebo saline solution injections in PREEMPT trials. • Transition probabilities generated from PREEMPT trials IPD. • Patients discontinuing Ona A follow transition probabilities for placebo injection group. • Resource use based on IBMS.
Differences with CDR submission	• Base-case population based on patients with CM who have ≥ 3 previous failed oral prophylactic therapies, and for whom medication overuse is appropriately managed. • BSC was assumed to encompass a range of interventional procedures and unlicensed medications and possibly consist of acute treatments only (i.e., no prophylactic medication). • Ona A discontinued if headache frequency is not reduced by ≥ 30% within first 24 weeks. • Ona A discontinued if patients transition to an EM health state after a year. • Utilities for the headache frequency health states were based on EQ-5D values from a European observational study of Ona A in patients with CM. • Nurse and consultant appointment costs based on ISD Scotland data.
Manufacturer's results	Base-case ICUR of £10,816 per QALY, based on incremental cost of £1,301 and a QALY gain of 0.12.
Issues noted by the review group	• The model is based on a post hoc subgroup analysis of 35% of the trial population. • It is uncertain whether the medication overuse patients in the clinical data were adequately managed. It is also uncertain whether this has an impact on efficacy results. • It is uncertain whether placebo injection efficacy is a proxy for BSC efficacy. • High uncertainty of implementation and the impact of positive stopping rule. In practice, patients may continue treatment despite meeting stopping criteria, increasing ICUR. • Assumption that patients with EM remain in the same health state for a year does not have clear rationale or plausibility. • Disutility associated with the administration of Ona A was not considered.
Results of reanalyses by the review group	Sensitivity analyses: • BSC efficacy increased by 1 HDPM: ICUR = £11.8 thousand per QALY. • Ona A efficacy reduced by 1 HDPM: ICUR = £18.9 thousand per QALY. • Patients with EM who cease treatment remain in the same health state for only 6 months: ICUR = £14.1 thousand per QALY. • 0.05 utility decrement for Ona A administration: ICUR = £13 thousand per QALY.
Recommendation	Accepted for restricted use in adults with CM whose condition has failed to respond to ≥ 3 prior oral prophylactic treatments, where medication overuse has been appropriately managed.

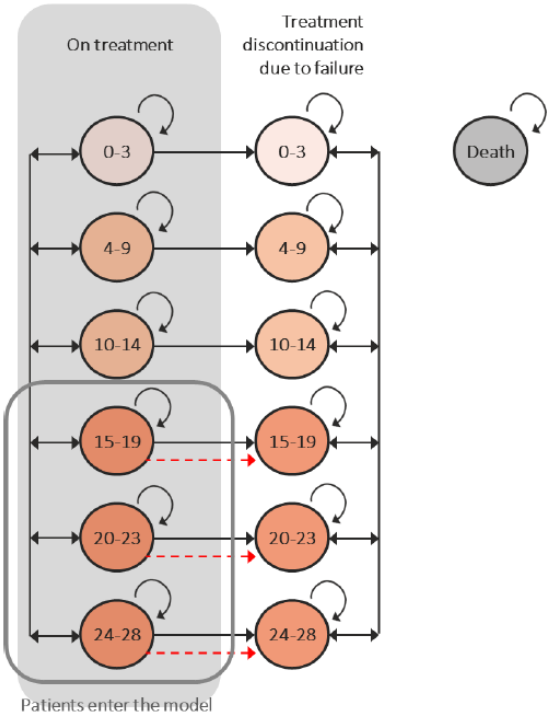
BSC = best supportive care; CAD = Canadian dollar; CDR = CADTH Common Drug Review; CM = chronic migraine; CUA = cost-utility analysis; EM = episodic migraine; GBP = British pounds sterling; HDPM = headache days per month; IBMS = International Burden of Migraine Study; ICUR = incremental cost-utility ratio; IPD = individual patient data; ISD = Information Services Division; SMC = Scottish Medicines Consortium.

Appendix 4: Reviewer Worksheets

Manufacturer's Model Structure

In the resubmission, the manufacturer submitted an updated cost-utility analysis that modelled 13 health states (Figure 1),[6] an increase from eight in the original submission.[4] Patients based on PREEMPT trial patients, who predominantly had chronic migraine (CM), receiving either onabotulinumtoxA (Ona A) or best supportive care (BSC) (or Ona A or topiramate in a scenario analysis), entered the model, and could transition every 12 weeks to health states of more- or less-frequent headaches over a three-year model time horizon. Headache frequency health states were treatment-dependent and the additional five health states included in the resubmission allowed the model to track potential changes in headache frequency for patients who discontinue treatment. A stopping rule based on treatment response was applied such that those who do not experience a reduction of at least 50% (30% in a scenario analysis) in headache frequency after two cycles of treatment (24 weeks) discontinued treatment (red arrows in Figure 1), reflecting current clinical guidelines[7] and reimbursement criteria.[5] In a scenario analysis, patients who achieved zero to three headaches per month for 24 weeks were also assumed to discontinue treatment, and restart treatment when headache frequency increased to at least 15 headaches per month once again. Patients could also transition to a death state based on the mortality risk of the general Canadian population. Treatment-related adverse events that occurred in more than 2% of patients in the PREEMPT trials were modelled, although these adverse events were not assumed to affect health utilities in the base-case analysis. Half of the adverse events were assumed to result in a physician visit.

Figure 1: Manufacturer's Model Structure



Note: The range of numbers presented in the diagram reflects the number of headache days per month (HDPM) (a month was assumed to be 28 days in the model). Patients typically start the model in health states with at least 15 HDPM, although up to a few patients start in the 10-to-14 HDPM to match PREEMPT program data in the manufacturer's base case, and FORWARD study data in the manufacturer's scenario analysis. Red arrows reflect patients who discontinue treatment due to lack of response.[6]

Source: Manufacturer's pharmacoeconomic submission.[6]

Table 12: Data Sources

Data Input	Description of Data Source	Comment
Baseline characteristics	Age and sex distribution parameters were from the ITT population in PREEMPT trials for the base-case comparison vs. BSC, and from FORWARD trial for the scenario analysis comparison vs. topiramate.	A small proportion of the ITT population in PREEMPT (1/1384 patients) and [redacted]. As the definition of CM includes at least 15 HDPM, those who have HDPM severity below this level at baseline should not be modelled.
Efficacy and natural history	Transition probabilities between HDPM health states for Ona A and BSC treatment groups were informed by PREEMPT trials. The transition probabilities for model cycles after 24 weeks were based on the trial results from the weeks 24 to 56 of the Ona A arm for Ona A transitions and from weeks 12 to 24 of the placebo arm for BSC transitions. The transition probabilities for the scenario analysis comparison vs. topiramate were informed by the FORWARD trials. The transition probabilities for model cycles after 24 weeks were based on the trial results from weeks 24 to 36 of the Ona A arm and topiramate arm, for Ona A transitions and topiramate transitions, respectively. Weeks 12 to 24 of the placebo arm from PREEMPT trials were used for transitions in discontinued patients.	Uncertain. Transition probabilities for BSC (based on oral medications) may differ from placebo treatment in PREEMPT trials (multiple injections to head). Due to the limitations of the FORWARD trial, the CADTH clinical reviewers determined that the comparative evidence between Ona A and topiramate based on this trial is uncertain. This is in contrast to an ICER ITC that indicated no statistically significant difference between Ona A and topiramate.[21] The validity of the FORWARD trial for the comparison vs. topiramate is therefore uncertain. Also, there is an inherent uncertainty associated with extrapolating short-term data from PREEMPT or FORWARD over the rest of the model time horizon. According to an expert consulted by CADTH, continued treatment would likely lead to maintenance of the achieved headache frequency rather than experiencing potential for continued improvement as modelled by the manufacturer.
Utilities	Health-utility values mapped from PREEMPT MSQ HRQoL data were used for base-case comparison vs. BSC. Scenario analyses explored the use of health utilities derived by the manufacturer from IBMS.[6] The same IBMS-derived utilities were used for the manufacturer's comparison of Ona A vs. topiramate.	Inappropriate. Mapped utilities are not recommended by CADTH.[10] EQ-5D health utilities for HDPM health states are available in literature.[9] Uncertain. Manufacturer's IBMS utility values were derived rather than using published observed values.[9] CADTH reanalysis 1a, 1b, and 1c, which tested alternate utility values based on published IBMS results, showed a larger ICUR compared with the manufacturer's scenario analysis, which used manufacturer-derived utility values. However, scenario analysis 1 for both the CADTH base case and CADTH topiramate comparison scenario analysis showed limited impact of this parameter.
Adverse events	For the base-case comparison vs. BSC, TEAE probabilities were informed by those adverse events arising in ≥ 2% of a treatment group in the	Inappropriate. Longer-term safety data would have been more appropriate.

Data Input	Description of Data Source	Comment
	safety population from week 24 to 36 of the PREEMPT trials. For the scenario analysis comparison vs. topiramate, TEAE probabilities were informed by those adverse events arising in ≥ 2% of a treatment group in the safety population during the first 36 weeks of the FORWARD trial.	 Uncertain. Due to the limitations of the FORWARD trial, the CADTH clinical reviewers could not draw a conclusion on the comparative evidence between Ona A and topiramate. The validity of the FORWARD trial for a comparison vs. topiramate is therefore uncertain. The validity of extrapolating adverse-event rates based on a 36-week period over the rest of the time horizon is uncertain. Values from both data sources were not appropriately transformed to fit the 12-week cycle length. A more appropriate method would have incorporated methods described in Fleurence and Hollenbeak's study.[11]
Mortality	Statistics Canada 2014-2016 life tables.	Appropriate.
Resource use	Resource use parameters were derived from IBMS.[8,22] Data from the second IBMS were explored in a scenario analysis.[23]	Generally appropriate, although there may be variation across the jurisdictions in Canada that results in some uncertainty, specifically relating to ED visits and hospitalization.
Costs	Unit costs were generally from Ontario Schedule of Benefits and Ontario Drug Benefits Program. Physician fee for Ona A injection cost was from the Alberta Health Care Insurance Plan. Hospitalization and ED unit costs were from CIHI. Average cost per unit of triptan was from IQVIA PharmaStat claims data.	Appropriate. Appropriate. As other jurisdictions may not cover physician fees associated with Ona A injection for headaches, (e.g., Ontario) the impact of omitting this fee should be explored in a scenario analysis. Acceptable sources. However, the ED unit cost from 2009 has not been inflated to reflect more recent context. 2016-2017 costs are available for Ontario from OCCI (ICD-10 codes G43.0 to G43.9).[24] Appropriate.

BSC = best supportive care; CIHI = Canadian Institute for Health Information; CM = chronic migraine; ED = emergency department; EQ-5D = EuroQol 5-Dimensions questionnaire; HDPM = headache days per month; HIT-6 = six-item Headache Impact Test; HRQoL = health-related quality of life; IBMS = International Burden of Migraine Study; ICD-10 = International Statistical Classification of Diseases and Related Health Problems, 10th Revision; ICER = Institute of Clinical and Economic Review; ICUR = incremental cost-utility value; ITC = indirect treatment comparison; ITT = intention-to-treat; MSQ = Migraine-Specific Quality of Life Questionnaire; OCCI = Ontario Case Costing Initiative; Ona A = onabotulinumtoxinA; TEAE = treatment-emergent adverse event.

Table 13: Manufacturer's Key Assumptions

Assumption	Comment
The most relevant comparator is BSC.	Inappropriate. According to an expert consulted by CADTH, topiramate and erenumab are other key therapies for the prophylaxis of CM. Although the manufacturer compared Ona A vs. topiramate in a scenario analysis, the manufacturer did not provide sufficient justification for not conducting a comprehensive analysis that compares all key therapies (Ona A, topiramate, erenumab, and BSC) when an indirect treatment comparison that incorporates these therapies is available.[21]
A placebo best approximates BSC.	Manufacturer assumed that BSC would be an unspecified group of acute-pain medications and would not include other prophylactic treatments in the submission.[6] This would be an inappropriate assumption based on a clinical expert's feedback provided to CADTH.
A time horizon of 3 years is long enough to sufficiently capture the costs and benefits of a treatment in patients diagnosed with CM.	Uncertain. Although CADTH considers a lifetime time horizon to be appropriate when modelling chronic conditions,[10] there is limited long-term evidence. According to an expert consulted by CADTH, a patient with CM could be treated for more than 10 years. The manufacturer has appropriately conducted scenario analyses of different time horizons, including 10-year and lifetime time horizons.
A model structure based on HDPM health states sufficiently captures a spectrum of health states that are meaningful to patients with CM.	Uncertain. The literature on the health-utility values associated with these HDPM-based health states is unclear as to whether the utility values are significantly different from each other.[9] Severity of headaches may need to be an additional consideration. An expert consulted by CADTH reported that headache severity may decrease with increasing frequency.
Population baseline characteristics differ by treatment groups.	Inappropriate. The differences between the treatment groups should be minimized such that the economic model results can be only attributed to consequences arising from different treatments that are compared. Consequently, the distribution of age, sex, and HDPM severity across the treatment groups should be the same.
Health-state utilities differ by treatment groups.	Inappropriate. Any differences in utilities stemming from treatment should be clearly captured by the model structure independent of treatment-assignment. The use of treatment-independent utilities as explored in one of the manufacturer's scenario analyses is more appropriate.
Adverse events were not assumed to lead to health-utility decrements in base case. In some scenario analyses, each adverse event was assumed to be associated with a utility decrement of 0.05.	Acceptable. The model tracked treatment-emergent adverse events of any grade instead of severe adverse events of grade 3 or 4. The relationship of these adverse events and health-utility decrement is uncertain. However, the clinical expert consulted by CADTH indicated that serious adverse events reported in PREEMPT are unlikely to be due to Ona A.[25] The arbitrary utility decrement of 0.05 used in the scenario analysis is inappropriate.
Transition probabilities for patients who discontinue treatment are based on the observed probabilities of patients with more than one prior prophylactic failure.	Uncertain. CADTH reviewers could not draw a conclusion from PREEMPT subgroup analyses as to whether different results could be expected by subgroups based on a history of prophylactic treatment failures.[25]
Patients who do not experience a reduction of ≥ 50% in HDPM in 24 weeks were assumed to discontinue Ona A in the base case.	Appropriate. Corresponds to the stopping rule used for Ontario's public drug plan.[5] As an expert consulted by CADTH also considered ≥ 30% reduction in HDPM to be a potential satisfactory response, the manufacturer's scenario analysis of discontinuation based on ≥ 30% treatment response rule is also appropriate.
Patients who achieve a headache frequency of EM (defined as below 15 HDPM) are assumed to continue Ona A treatment.	Uncertain. Patients with EM are not indicated for prophylactic treatment with Ona A. According to an expert consulted by CADTH, patients who discontinue treatment for this reason typically relapse and qualify for prophylactic treatment

Assumption	Comment
	for CM within a month. The manufacturer's scenario analysis whereby patients who achieve 0 to 3 HPDM discontinued prophylactic treatment does not sufficiently capture this clinical practice. However, it is unknown whether discontinuations due to EM occur across all Canadian jurisdictions.
Drug-dose wastage was not assumed for base-case analysis.	Inappropriate. This would lead to a reduced cost and ICUR associated with Ona A.
Half of treatment-emergent adverse events in the model were assumed to lead to a physician visit.	Uncertain. The model tracked treatment-emergent adverse events of any grade instead of severe adverse events of grade 3 or 4. The relationship of these adverse events and health care resource use is uncertain.

BSC = best supportive care; CM = chronic migraine; EM = episodic migraine; HDPM = headache days per month; ICUR = incremental cost-utility ratio; Ona A = onabotulinumtoxinA.

Manufacturer's Results

The base-case results are presented in Table 2. According to the manufacturer's cost-effectiveness acceptability curve, Ona A had 64% probability of being cost-effective at a WTP threshold of $50,000 per quality-adjusted life-year (QALY), and a 77% probability of being cost-effective at a WTP threshold of $100,000 per QALY.[6] Manufacturer's scenario analyses are presented in Table 14. The pharmacoeconomic model was most sensitive to a change to societal perspective, time horizon, different target population, treatment stopping rules, consideration of drug wastage, the use of treatment-independent health utilities, and comparisons to topiramate.

Table 14: Manufacturer's Scenario Analyses: Mean Probabilistic Results

Scenario	Incremental Cost per QALY ($)
Perspective	
Societal perspective	24,046
Discount rate	
0% discount rate	34,501
3% discount rate	34,617
Time horizon	
5-year time horizon	30,814
10-year time horizon	26,972
Lifetime time horizon	26,530
Target population	
Population with ≥ 1 prior oral prophylactic failures	26,672
Population with ≥ 2 prior oral prophylactic failures	29,187
Population with ≥ 3 prior oral prophylactic failures	29,974
Treatment stopping rule	
Stop treatment if < 30% reduction in headache days after 24 weeks	33,982
Do not stop treatment based on response	39,564
Stop treatment if headache frequency reduces to 0 to 3 headaches per month for 24 weeks. Restart treatment when headache frequency increases to ≥ 15 headaches per month.	29,161
Health-state utilities	
Treatment-independent utilities	45,324

Scenario	Incremental Cost per QALY ($)
IBMS-derived utilities	36,128
Resource use and cost	
Consider drug wastage	41,350
Estimate health care resource use from the second IBMS[23]	34,237
Assume no physician visit for TEAEs	34,029
Assume a physician visit per TEAE	34,252
Comparison vs. topiramate	
Ona A vs. Topiramate; discontinuation rate from FORWARD trial.	13,283
Ona A vs. Topiramate; discontinuation due to AEs only.	16,053
Ona A vs. Topiramate; discontinuation adjusted using BOCF.	13,011

AE = adverse events; BOCF = baseline observation carried forward; BSC = best supportive care; IBMS = International Burden of Migraine Study; Ona A = onabotulinumtoxinA; QALY = quality-adjusted life-year; TEAE = treatment-emergent adverse events.

CADTH Common Drug Review Reanalyses

Additional information for the reanalyses CADTH identified in the main body of the report is provided below.

CADTH Base-Case Reanalyses:

1. **Alternate treatment-independent utility values directly based on, instead of derived from, the International Burden of Migraine Study (IBMS):**

(a) by headache days per month (HDPM) health states, based on IBMS survey respondents who completed EuroQol 5-Dimensions questionnaire (EQ-5D) and six-item Headache Impact Test (HIT-6).

Mean EQ-5D health-utility values for the model's headache frequency health states were sourced from IBMS survey respondents who completed EQ-5D and HIT-6 (Table 15). The utility values were assumed to be the same regardless of the patient's treatment status. Standard errors of the utility values were derived from the same study to inform the probabilistic analysis.

(b) by HDPM health states, based on IBMS survey respondents who completed EQ-5D and Migraine-Specific Quality of Life Questionnaire (MSQ).

Similarly to analysis 1A, mean EQ-5D health-utility values for the model's headache frequency health states were sourced from IBMS survey respondents who completed EQ-5D and MSQ (Table 15).

(c) by CM and episodic migraine (EM) health states, based on IBMS survey respondents.

As IBMS found significant difference in utility values between EM and CM, but not across headache frequency health states,[9] mean EQ-5D health-utility values for EM (< 15 HDPM; 0.68) and CM (≥ 15 HDPM; 0.46) health states were applied to headache frequency health states corresponding to EM and CM. The utility values were assumed to be the same regardless of the patient's treatment status and HDPM within the CM and EM states.

Table 15: EuroQol 5-Dimensions Questionnaire Health Utilities From Gillard et al. (2012)[9]

Health State	Mean Utility of EQ-5D and HIT-6 Respondents (SE)	Mean Utility of EQ-5D and MSQ Respondents (SE)
0 to 3 HDPM	0.700 (0.008)	0.716 (0.007)
4 to 9 HDPM	0.633 (0.013)	0.647 (0.014)
10 to 14 HDPM	0.608 (0.025)	0.555 (0.031)
15 to 19 HDPM	0.51 (0.053)	0.606 (0.039)
20 to 23 HDPM	0.468 (0.042)	0.450 (0.056)
24 to 28 HDPM	0.300 (0.045)	0.296 (0.048)

EQ-5D = EuroQol 5-Dimensions questionnaire; HDPM = headache days per month; HIT-6 = six-item Headache Impact Test; MSQ = Migraine-Specific Quality of Life Questionnaire; SE = standard error.

Source: Gillard et al. (2012).[9]

2. **Alternate adverse-event probabilities based on the 24-week double-blind period of PREEMPT trials, converted to 12-week cycle probabilities using Fleurence and Hollenbeak's methodology.[11]**

Overall adverse-event probabilities based on a 24-week double-blind period of PREEMPT trials were applied to the base-case analysis, reflecting the most long-term double-blinded comparative evidence available. This replaced the modelling of adverse events independently. The overall adverse-event probabilities were converted to fit the modelled 12-week cycle length. Of the patients receiving Ona A and BSC, 16.0% and 6.6%, respectively, were estimated to experience an adverse event during each 12-week cycle.

3. **Same age, sex, and headache frequency baseline characteristics assumed for all treatment groups based on both arms of PREEMPT trials; no patients below 15 HDPM at baseline.**

Baseline headache frequency distribution was altered such that patients below 15 HDPM do not enter the model. Age, sex, and headache frequency distribution parameters were also assumed to be the same for all treatment groups based on the PREEMPT trial (age: mean = 41.3 years, standard deviation = 10.54; 86.4% female; Table 16). The same baseline characteristics were also assumed for the topiramate comparison scenario analysis.

Table 16: Baseline Distribution of Headache Frequency

Health State	Proportion of Patients (%)
0 to 3 HDPM	0
4 to 9 HDPM	0
10 to 14 HDPM	0
15 to 19 HDPM	52.97
20 to 23 HDPM	28.45
24 to 28 HDPM	18.58

HDPM = headache days per month.

4. **Alternate transition probabilities:**

(a) transition probabilities of patients who discontinued treatment based on the intention-to-treat (ITT) population.

Patients who discontinue treatment followed transition probabilities of the ITT population from PREEMPT trials instead of the transition probabilities of a subgroup of patients from the same study with a prior prophylactic failure at baseline.

(b) long-term treatment transition probabilities (beyond 24 weeks) based on the ITT population.

Beyond the first 24 weeks of the time horizon, patients on treatment followed transition probabilities of the ITT population instead of the transition probabilities based on a subgroup of patients who continued treatment based on 50% or 30% headache frequency reduction response criteria.

5. **Long-term plateauing and maintenance of headache frequency reduction efficacy.**

Transition probabilities for model cycles beyond the first 24 weeks and for patients who discontinue initial treatment were restricted such that the patients do not improve or worsen; patients maintain the health state and do not transition to health states with higher or lower HDPM.

6. **Updated ED cost and drug-wastage consideration.**

ED unit cost was updated to 2016-2017 ambulatory care cost for migraine-associated cases (defined by International Statistical Classification of Diseases and Related Health Problems, 10th Revision, codes G43.0 to G43.9[22]) from Ontario Case Costing Initiative (mean: $251; SD: $148).[24] The option in the manufacturer's model to consider drug wastage was also enabled to consider associated increases in treatment cost.

CADTH Scenario Analysis on the CADTH Base Case:

The following scenario analyses were additionally conducted to explore sources of uncertainties that CADTH was unable to address in the CADTH base case and scenario analysis comparison of Ona A and topiramate:

Scenario analysis 1: IBMS utility values derived by the manufacturer incorporated, instead of analysis 1c.

Scenario analysis 2: < 30% headache frequency reduction stopping rule.

Scenario analysis 3: 10-year time horizon.

Scenario analysis 4: No physician administration cost for Ona A injection.

Scenario analysis 5:

a. Analysis 4a incorporated instead of analysis 4c.
b. Analysis 4b incorporated instead of analysis 4c.
c. Analysis without incorporating analysis 4c.

Table 17: CADTH Scenario Analyses (OnabotulinumtoxinA vs. Best Supportive Care)

	Analysis	Comparator	Cost ($)	QALYs	ICUR ($ per QALY Gained)
S1	B1 and IBMS utility derived by the manufacturer	Ona A	8,082	1.86	-
		BSC	3,915	1.83	-
		Incremental	*4,167*	*0.03*	*137,063*
S2	B1 and < 30% stopping rule	Ona A	9,114	1.79	-
		BSC	3,890	1.74	-
		Incremental	*5,224*	*0.05*	*113,501*
S3	B1 and 10-year time horizon	Ona A	19,310	5.53	-
		BSC	12,184	5.43	-
		Incremental	*7,126*	*0.09*	*75,971*
S4	B1 and no Ona A administration cost	Ona A	7,603	1.77	-
		BSC	3,925	1.74	-
		Incremental	*3,678*	*0.03*	*119,349*
S5a	B1 and reanalysis 4a instead of 4c	Ona A	8,085	1.76	-
		BSC	3,917	1.73	-
		Incremental	*4,168*	*0.03*	*135,692*
S5b	B1 and reanalysis 4b instead of 4c	Ona A	8,066	1.77	-
		BSC	3,923	1.73	-
		Incremental	*4,143*	*0.03*	*131,206*
S5c	B1 without 4c	Ona A	8,055	1.76	-
		BSC	3,905	1.73	-
		Incremental	*4,150*	*0.03*	*134,755*

BSC = best supportive care; IBMS = International Burden of Migraine Study; ICUR = incremental cost-utility ratio; Ona A = onabotulinumtoxinA; QALY = quality-adjusted life-year.

CADTH Reanalysis for Topiramate Scenario

Additional information specific to the CADTH reanalyses 2a and 2b for the comparison of Ona A and topiramate are provided below (the other reanalyses are as per the CADTH base-case reanalyses described above) with the results captured in Table 18:

1. **Alternate adverse-event data:**

(a) **alternate adverse-event probabilities based on the 36-week FORWARD trial period, converted to 12-week cycle probabilities using Fleurence and Hollenbeak's methodology.**[11]

Overall adverse-event probabilities based on the 36-week period of the FORWARD trial were converted to fit the modelled 12-week cycle length. Of the patients receiving Ona A and topiramate, 19.4 % and 40.4%, respectively, were estimated to experience an adverse event during each 12-week cycle.

(b) **corrected adverse-event disutility calculation, adverse-event rates are based on proportion of on-treatment patients rather than on proportion of patients that enter model.**

QALY calculations in the manufacturer's model subtracted the summed products of adverse-event probabilities and disutilities from QALYs associated with patients on Ona A or BSC treatment. As the adverse-event probabilities were not weighted to the proportion of patients alive in each cycle, they were appropriately weighted to this proportion for this reanalysis.

Table 18: CADTH Reanalysis (OnabotulinumtoxinA vs. Topiramate)

	Analysis	Comparator	Cost ($)	QALYs	ICUR ($ per QALY Gained)
1a	IBMS utility based on EQ-5D and HIT-6 survey responders	Ona A	7,283	1.68	-
		Topiramate	3,945	1.61	-
		Incremental	*3,338*	*0.07*	*46,885*
1b	IBMS utility based on EQ-5D and MSQ survey responders	Ona A	7,279	1.70	-
		Topiramate	3,940	1.63	-
		Incremental	*3,339*	*0.07*	*46,644*
1c	IBMS utility (CM vs. EM)	Ona A	7,283	1.77	-
		Topiramate	3,946	1.72	-
		Incremental	*3,337*	*0.05*	*69,259*
2a	Updated adverse events	Ona A	7,280	1.90	-
		Topiramate	3,930	1.79	-
		Incremental	*3,350*	*0.11*	*29,371*
2b	Corrected adverse-event disutility calculations	Ona A	7,279	1.64	-
		Topiramate	3,940	1.56	-
		Incremental	*3,339*	*0.08*	*39,969*
3	Updated baseline characteristics	Ona A	7,367	1.93	-
		Topiramate	3,766	1.81	-
		Incremental	*3,602*	*0.12*	*30,491*
4a	Post-treatment discontinuation transition probabilities based on ITT	Ona A	7,088	1.93	-
		Topiramate	3,942	1.79	-
		Incremental	*3,146*	*0.14*	*22,117*
4b	Transition probabilities beyond 24 weeks based on ITT	Ona A	7,157	1.91	-
		Topiramate	3,761	1.80	-
		Incremental	*3,396*	*0.11*	*30,906*
4c	4A and 4B	Ona A	6,962	1.94	-
		Topiramate	3,755	1.81	-
		Incremental	*3,207*	*0.13*	*24,168*
5	Long-term efficacy plateau and maintenance	Ona A	6,884	1.92	-
		Topiramate	3,935	1.79	-
		Incremental	*2,948*	*0.13*	*22,175*
6	Updated ED cost and drug wastage	Ona A	8,167	1.90	-
		Topiramate	4,220	1.79	-
		Incremental	*3,947*	*0.11*	*34,645*

CM = chronic migraine; ED = emergency department; EQ-5D = EuroQol 5-Dimensions questionnaire; EM = episodic migraine; HDPM = headache days per month; HIT-6 = six-item Headache Impact Test; IBMS = International Burden of Migraine Study; ICUR = incremental cost-utility ratio; ITT = intention-to-treat; MSQ = Migraine-Specific Quality of Life Questionnaire; Ona A = onabotulinumtoxinA; QALY = quality-adjusted life-year.

Table 19: CADTH Scenario Analyses (OnabotulinumtoxinA vs. Topiramate)

	Analysis	Comparator	Cost ($)	QALYs	ICUR ($ per QALY Gained)
S1	T1 and IBMS utility derived by the manufacturer	Ona A	7,805	1.95	-
		Topiramate	4,157	1.83	-
		Incremental	*3,648*	*0.12*	*30,491*
S2	T1 and < 30% stopping rule	Ona A	9,007	1.86	-
		Topiramate	4,217	1.73	-
		Incremental	*4,790*	*0.13*	*35,745*
S3	T1 and 10-year time horizon	Ona A	16,203	5.83	-
		Topiramate	12,522	5.43	-
		Incremental	*3,681*	*0.40*	*9,239*
S4	T1 and no Ona A administration cost	Ona A	7,268	1.86	-
		Topiramate	4,162	1.73	-
		Incremental	*3,106*	*0.13*	*24,837*
S5a	T1 and reanalysis 4a instead of 4c	Ona A	7,802	1.86	-
		Topiramate	4,152	1.73	-
		Incremental	*3,650*	*0.13*	*29,170*
S5b	T1 and reanalysis 4b instead of 4c	Ona A	7,681	1.86	-
		Topiramate	4,152	1.73	-
		Incremental	*3,529*	*0.12*	*28,489*
S5c	T1 without 4c	Ona A	7,678	1.86	-
		Topiramate	4,147	1.74	-
		Incremental	*3,531*	*0.12*	*28,390*

IBMS = International Burden of Migraine Study; ICUR = incremental cost-utility ratio; Ona A = onabotulinumtoxinA; QALY = quality-adjusted life-year.

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