Common Drug Review

Pharmacoeconomic Review Report

July 2015

Drug	onabotulinumtoxinA for injection (Botox)
Indication	For the prophylaxis of headaches in adults with chronic migraine (≥ 15 days per month with headache lasting 4 hours a day or longer)
Listing request	Prophylaxis of headaches in adults with chronic migraine (≥ 15 days per month with headache lasting 4 hours a day or longer) who have failed (i.e., lack of efficacy, intolerance, or clinical contraindication) ≥ 3 prior oral prophylactic medications. Patients who have not obtained an adequate treatment response (≥ 30% reduction in days of headache per month) after 2 treatment cycles should be discontinued from further therapy.
Manufacturer	Allergan Inc.

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TABLE OF CONTENTS

ABBREVIATIONS iii

EXECUTIVE SUMMARY OF THE PHARMACOECONOMIC SUBMISSION 1

REVIEW OF THE PHARMACOECONOMIC SUBMISSION 3
1. Introduction 3
2. Methods 4
3. Results 10
4. Discussion 14
5. Conclusions 17

APPENDIX 1: COST COMPARISON TABLE 18
APPENDIX 2: SUMMARY OF KEY OUTCOMES 20
APPENDIX 3: ADDITIONAL INFORMATION 21
APPENDIX 4: SUMMARY OF CLINICAL INFORMATION 22
APPENDIX 5: OTHER HEALTH TECHNOLOGY ASSESSMENT FINDINGS 25

REFERENCES 27

Tables

Table 1: Summary of the Manufacturer's Economic Submission iv
Table 2: Summary of Adverse Event Profile, Full Population (at Week 24) 6
Table 3: Summary of Adverse Event Profile, Subpopulation (at Week 24) 6
Table 4: Model Utility Values for Each Health State 8
Table 5: Summary of Results of the Manufacturer's Base Case 10
Table 6: Summary of Results of the Manufacturer's Scenario Analysis of the Full Population 10
Table 7: CDR Analyses — Revised OnabotulinumtoxinA Consultation Price 12
Table 8: CDR Analyses — Include Administration Cost 12
Table 9: CDR Analyses — Drug Acquisition Cost 13
Table 10: CDR Analyses — Event Treatment Costs: Hospitalization and Emergency Room Visits 13
Table 11: CDR Analyses – Event Treatment Costs: Hospitalization and Emergency Room Visits 13
Table 12: CDR Reanalysis — Incorporating Reanalyses 1, 2, and 3 13
Table 13: CDR Analyses – Price Analyses for OnabotulinumtoxinA 14
Table 14: Key Limitations of the Manufacturer's Economic Submission 15
Table 15: Cost Comparison Table for Drugs Used for Prophylaxis of Chronic Migraine 18
Table 16: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive Is OnabotulinumtoxinA Relative to Best Supportive Care? 20
Table 17: Submission Quality 21
Table 18: Author Information 21
Table 19: Summary of Headache Days for Botox Patients From the Pooled PREEMPT ITT Data (Baseline to Week 12) 22
Table 20: Summary of Headache Days for Botox Patients From the Pooled PREEMPT ITT Data (Week 12 to Week 24) 23
Table 21: Summary of Headache Days for Botox Patients From the Pooled PREEMPT Subpopulation Data (Baseline to Week 12) 23

Table 22: Summary of Headache Days for Botox Patients From the Pooled PREEMPT Subpopulation Data (Week 12 to Week 24) 24
Table 23: Other Health Technology Assessment Organizations' Findings 25

Figure

Figure 1: Model Diagram, Primary Economic Model (Markov Structure) 5

ABBREVIATIONS

AE	adverse event
BSC	best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CDEC	Canadian Drug Expert Committee
CDR	CADTH Common Drug Review
CM	chronic migraine
CUA	cost-utility analysis
EM	episodic migraine
ER	emergency room
HC	Health Canada
HDPM	headache days per month
HIT-6	Headache Impact Test-6
HTA	health technology assessment
IBMS	International Burden of Migraine Study
ICHD	International Classification of Headache Disorders
ICUR	incremental cost-utility ratio
INESSS	L'Institut national d'excellence en santé et en services sociaux
ITT	intention-to-treat
MSQ	Migraine-Specific Quality of Life Questionnaire
NICE	National Institute for Health and Care Excellence
PBAC	Pharmaceutical Benefits Advisory Committee
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
SMC	Scottish Medicines Consortium
U	unit
VAS	visual analogue scale

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	onabotulinumtoxinA (Botox)
Study Question	From the perspective of the public payer in Canada, what is the cost-utility of onabotulinumtoxinA as compared with best supportive care (BSC) for the prophylaxis of headache in adults who have failed three or more oral prophylactic medications? The manufacturer also undertook a scenario analysis of onabotulinumtoxinA in the full Health Canada indication as per CDR guidelines.
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adults with CM, ≥ 15 HDPM with headache lasting 4 hours a day or longer) who have failed (i.e., lack of efficacy, intolerance or clinical contraindication) 3 or more prior oral prophylactic medications As indicated above, the manufacturer undertook a scenario analysis of the full population — CM without treatment failure.
Treatment	onabotulinumtoxinA
Outcome	QALY
Comparators	BSC (appears to be placebo + acute treatments)
Perspective	Public payer
Time Horizon	3 years
Manufacturer's Results (Base Case)	$28,940 per QALY (full indication population) $25,470 per QALY (subpopulation)
Key Limitations and CDR Estimate(s)	• The key limitation of the manufacturer's economic submission is whether the submitted model presents a good representation of the chronic nature of the disease and expected treatment. The modelling of CM is based on assumptions regarding patients with EM continuing treatment with onabotulinumtoxinA, lack of clarity around discontinuation of treatment, use of a "30% reduction in headache days" stopping rule, and the choice of a 3-year time horizon for a chronic condition. • The costs associated with physician visits, drug administration, and drug acquisition for onabotulinumtoxinA were likely underestimated in the economic model, which bias the results in favour of onabotulinumtoxinA. • Given the limitations identified, the likely ICUR is uncertain. When accounting for more likely cost inputs, CDR calculated ICURs in the range of $42,000 to $47,000 per QALY.

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; QALY = quality-adjusted life-year.

EXECUTIVE SUMMARY OF THE PHARMACOECONOMIC SUBMISSION

Background

OnabotulinumtoxinA (Botox) was submitted to CDR for the prophylaxis of headaches in adults with chronic migraine (CM, ≥ 15 days per month with headache lasting four hours a day or longer). The manufacturer has requested listing in a subpopulation of patients that have failed to respond to treatment with three or more oral prophylactic agents. OnabotulinumtoxinA is administered as a minimum of 31 injections and a maximum of 39 injections of five units (U) per injection to the head and neck every 12 weeks (total: 155 U to 195 U per administration). The submitted price is listed at $3.57 per U, with the pack sizes 50 U, 100 U, and 200 U. Given that the vials cannot be reused[1] (therefore incurring wastage), the cost per administration is $714.

OnabotulinumtoxinA was previously reviewed by CDR in 2012 for the treatment of urinary incontinence due to neurogenic detrusor overactivity resulting from neurogenic bladder associated with multiple sclerosis (MS) or subcervical spinal cord injury (SCI). CDEC recommended that onabotulinumtoxinA be listed with conditions.[2]

Summary of Economic Analysis

The manufacturer submitted a cost-utility analysis (CUA) of onabotulinumtoxinA compared with best supportive care (BSC) for the prophylaxis of headache in adults who have failed three or more prior oral prophylactic medications; this represents a subpopulation of the Health Canada (HC) indication, as the HC indication does not limit use to patients who have failed prior therapy. The analysis was based on a Markov model with seven health states, six based on the number of headache days experienced per 28-day period (zero to three days, four to nine days, 10 to 14 days, 15 to 19 days, 20 to 23 days, and 24 days or more) and one discontinuation state. Efficacy data were derived from pooling data from the PREEMPT studies (PREEMPT-1 and PREEMPT-2). Patients entered the model at one of the three health states defined as CM (≥ 15 days headache days per month [HDPM]) and transitioned to the other health states based upon patient-level data from the PREEMPT studies. The manufacturer captured treatment costs associated with onabotulinumtoxinA and BSC, as well as the costs of medical resource utilization. The manufacturer included a scenario analysis from the societal perspective, taking into account lost productivity. Utility values for each health state were obtained through mapping quality-of-life data captured in the clinical trials to the EuroQol 5 dimensions (EQ-5D) utility instrument. Scenario analyses using survey-generated EQ-5D utility values were also undertaken. The time horizon for the analysis was set at three years, with a cycle length of 12 weeks.

Results of Manufacturer's Analysis

The result of the manufacturer's analysis of the full HC population was an ICUR of $28,940 per QALY gained for onabotulinumtoxinA compared with BSC. For the analysis of the requested subpopulation (patients who failed to respond to treatment with three or more oral prophylactic agents), the ICUR was $25,470 per QALY gained.

Interpretations and Key Limitations

The key limitation of the manufacturer's submitted economic evaluation is whether the submitted economic evaluation presents a good representation of the chronic nature of the condition and expected treatment, where key assumptions include:

- The model included health states that represent episodic migraine (EM, < 15 HDPM), a population for which onabotulinumtoxinA is not indicated. EM reflects a distinct clinical entity different from CM. Patients improving to episodic states continued to receive treatment, incurring the costs of treatment and the clinical benefits. The effects of including patients no longer in CM could overestimate the benefits of onabotulinumtoxinA.
- The choice of a 30% stopping rule is arbitrary. Improvements of 25%, 50%, and 75% were captured in the clinical trials, as opposed to 30%. Treatment guidelines and CDR clinical guidance has indicated that a 50% reduction or return to the EM health state is the clinical goal of treatment (no statistically significant difference in PREEMPT-1).
- CM, defined as ≥ 15 HDPM with headache lasting 4 hours a day or longer, is currently a long-term condition; however, a three-year time horizon was used in the economic model. The manufacturer stated that onabotulinumtoxinA is a preventive therapy, and continued treatment is needed for most patients in order to maintain treatment response and benefit, similar to any other preventive medication.[3] This leads to the assumption that a longer time horizon may be more appropriate, where patients are expected continue on onabotulinumtoxinA indefinitely. Long-term use of onabotulinumtoxinA has not been studied, so it is unclear whether treatment effects would be maintained over time.
- The costs associated with physician visits, drug administration, and drug acquisition for onabotulinumtoxinA were likely underestimated in the economic model.

It is also unclear whether patients who "discontinued" treatment entered an absorbing state or were permitted to cycle back into the model. How recurrence of chronic states is included was not clearly detailed.

Results of CADTH Common Drug Review Analysis

The manufacturer made several assumptions regarding the structure of the model which did not permit modification for reanalyses that would provide a more likely estimate of the cost-effectiveness of onabotulinumtoxinA. Assumptions regarding the cost of physician visits, the cost of administration, and the cost of drug acquisition for onabotulinumtoxinA were considered — all of which increased the ICUR between 10% and 28% individually from the manufacturer's base-case results for both the full and restricted populations, and between 63% and 65% when considered collectively ($42,000 to $47,000 per QALY).

Issues for Consideration

- There is an unmet clinical need in patients who have failed prior oral prophylactic therapies, as no other treatments are currently indicated.
- There is the potential for use beyond the current indication being reviewed, as onabotulinumtoxinA is approved for eight clinical indications for use.

Conclusions

Given the limitations of the model structure, a full exploration of CDR identified limitations was not possible. Consequently, there is some uncertainty regarding the cost-effectiveness of onabotulinumtoxinA.

REVIEW OF THE PHARMACOECONOMIC SUBMISSION

1. INTRODUCTION

1.1 Study Question

"From the perspective of the public payer in Canada, what is the cost-utility of Botox as compared to Best Supportive Care (BSC), for the prophylaxis of headache in adults who have failed three or more oral prophylactic medications?" (*Page 7 of the Manufacturer's Pharmacoeconomic [PE] report*[4])

To be in line with the requested indication, explicit reference to chronic migraine (CM) may have been more appropriate.

1.2 Treatment

OnabotulinumtoxinA is administered as a minimum of 31 and a maximum of 39 injections of five units (U) per injection (total: 155 U to 195 U) at sites on the neck and head every 12 weeks. A stopping rule has been proposed by the manufacturer.

1.3 Comparators

The manufacturer stated that BSC (defined as the use of acute medications as needed) was the comparator in this submission. This comparator was used in both the restricted and full patient populations. Although the manufacturer deemed this appropriately representative of the BSC population, the PREEMPT clinical trials did not include an active comparator arm (placebo). However, the manufacturer stated that *"[onabotulinumtoxinA] would not replace any other headache prophylaxis therapy*;" thus, the comparison appears to have been onabotulinumtoxinA + BSC versus placebo + BSC.

1.4 Type of Economic Evaluation

The manufacturer undertook a CUA. This is appropriate as per the Canadian Agency for Drugs and Technology in Health's (CADTH's) *Guidelines for Economic Evaluations of Health Technologies: Canada*.[5]

The analysis takes a public payer perspective. This is appropriate as per CADTH guidelines.[5] A scenario analysis was conducted from the societal perspective.

1.5 Population

The HC indication for onabotulinumtoxinA is for prophylactic treatment of adults with CM (≥ 15 headache days per month [HDPM] with headache lasting four hours a day or longer). The manufacturer requested reimbursement of a subgroup of patients within the Health Canada (HC) indication — patients with CM who have failed three or more prior oral prophylactic medications.

As per CADTH Common Drug Review (CDR) guidance (CDR Update – Issue 83) the manufacturer included an analysis of the full CM population, as identified in the approved HC indication.

CDR clinical input has indicated that it is likely that onabotulinumtoxinA would only be considered for patients that had failed all other treatment types (including behavioural therapies).

2. METHODS

The manufacturer presented its primary economic evaluation for the subpopulation of patients that had failed three or more prior oral prophylactic therapies, as well a scenario analysis for the full HC-indicated population. CDR critiqued both populations.

2.1 Model Structure

The manufacturer's CUA employed a Markov State Transition approach. Patient-level data from the two PREEMPT studies were pooled to populate the model. The 12-week cycle time used in the model is consistent with the stated dosing interval in both PREEMPT studies. The defined health states (Figure 1) correspond to the number of headache days per 28-day period experienced by a patient based on the International Classification of Headache Disorders – 2nd edition (ICHD-2) and revised ICHD-2 (ICHD 2-R) reports and papers by Lipton et al.[6,7] that explore when prophylactic medications should be given and at what point CM occurs. Other economic studies of onabotulinumtoxinA have used the same set of health states,[8,9] although Batty et al.[8] is more comprehensive and includes an "off-treatment" to allow patients to cycle in and out of treatment. Justification for the health states past 15 HDPM (as per CM) and discontinuations were based on assumptions informed from the PREEMPT studies.

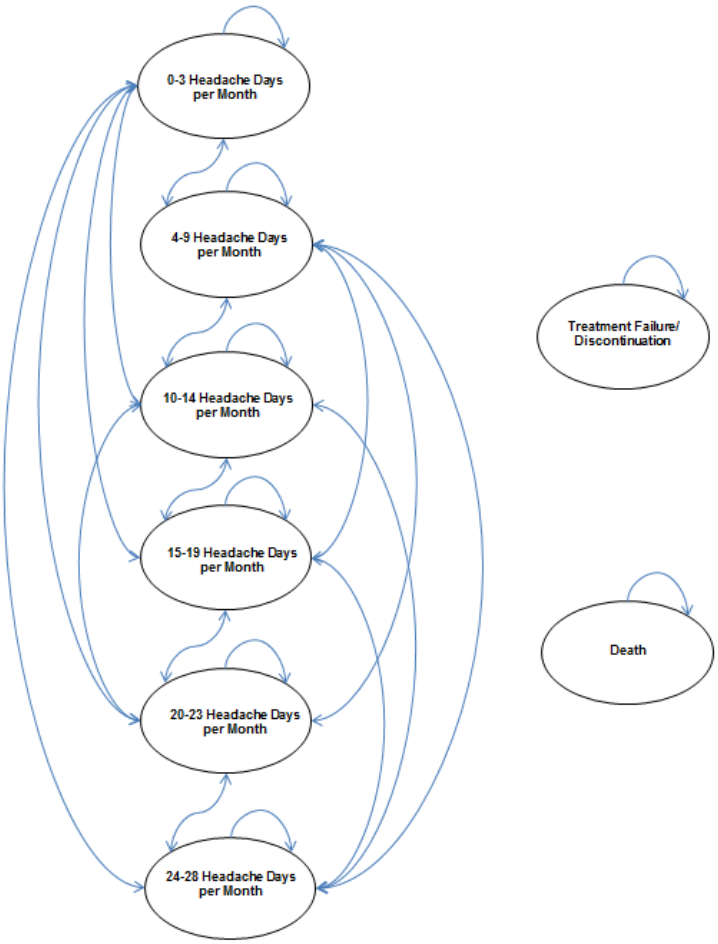
Patients entered the model at one of the three health states defined as CM (≥ 15 HDPM) and transitioned to the other health states. Transition probabilities for both arms were based on patient-level data from the PREEMPT studies up to 24 weeks. Beyond 24 weeks, the average transitional probabilities observed by onabotulinumtoxinA patients in the extension study were used, while the BSC arm used the same transitions as seen between weeks 12 and 24 in the double-blind portion of the PREEMPT studies.

2.2 Clinical Inputs

Efficacy data from the Intention-to-Treat (ITT) population in the two PREEMPT studies were used in the full population model, and a subpopulation of patients from the two PREEMPT studies were used in the requested indication model. The ITT population includes both patients who have used at least one oral migraine medication (64%) and patients who have not (36%). The model for the requested indication included approximately 35% of patients from the PREEMPT studies.

The manufacturer did consider undertaking a crude comparison of onabotulinumtoxinA and topiramate, as it indicated that topiramate is the only medication currently licensed for migraine prophylaxis in Canada even though the safety and efficacy of topiramate in CM has not been established. The crude comparison of the two PREEMPT trials with the two trials of topiramate versus placebo[10,11] indicated that there were a number of differences between the two populations, although the manufacturer stated that it would expect the estimated ICUR to decrease if topiramate patient data was available to inform the comparator arm. CDR did not assess this comparison given the inherent differences in the studies.

FIGURE 1: MODEL DIAGRAM, PRIMARY ECONOMIC MODEL (MARKOV STRUCTURE)



Note: Model diagram in the manufacturer's economic model differs from this diagram, indicating that treatment failure and discontinuation may not be an absorbing health state.
Source: Manufacturer's Pharmacoeconomic Report, Figure 4, page 17.[4]

2.2.1 Efficacy

The clinical information supplied for the model will not be found in the CDR Clinical Report. The information presented was pooled data from the two PREEMPT studies (PREEMPT-1 and PREEMPT-2). It appears that post hoc subgroup analyses were undertaken on the pooled data for the frequency of headache days. This individual patient data was used to populate the transition matrices of the model. This information is provided in more detail in Appendix 4: Summary of Clinical Information.

The results of several end points differed between the PREEMPT-1 and PREEMPT-2 studies (see CDR Clinical Report), and although methodologically, the pooling of the data for the economic evaluation is appropriate, it would have been of benefit to CDR if scenario analyses had been presented with the individual results of both studies.

2.2.2 Harms

The nature and frequency of adverse events (AEs) were similar for both treatment groups in the pooled analysis of both the full population (Table 2) and the subpopulation (Table 3). The main AEs experienced by patients in the onabotulinumtoxinA group were neck pain, muscular weakness, and eyelid ptosis (common to the full and subpopulations), as well as injection-site pain (full) and myalgia (subpopulation). The manufacturer reported that the AE profile did not differ between studies. Although treatment-related AEs were proportionally more frequent in onabotulinumtoxinA patients, CDR clinical guidance has indicated that this is unlikely to increase other provincially funded health care costs, given the nature of the AEs.

TABLE 2: SUMMARY OF ADVERSE EVENT PROFILE, FULL POPULATION (AT WEEK 24)

Parameter	Ona A	Placebo
Total patients in study	688	696
Patients with AEs, n (%)	429 (62)	358 (51)
Patients with treatment-related AEs, n (%)	202 (29)	88 (13)
Patients with SAEs, n (%)	33 (4.8)	16 (2.3)
Discontinuation due to AE, n (%)	26 (3.8)	8 (1.1)

AE = adverse event; n = number; Ona A = onabotulinumtoxinA; SAE = serious adverse event.
Source: Dodick et al.[12]

TABLE 3: SUMMARY OF ADVERSE EVENT PROFILE, SUBPOPULATION (AT WEEK 24)

Parameter	Ona A	Placebo
Total patients in study	233	246
Patients with AEs, n (%)	150 (64)	139 (57)
Patients with treatment-related AEs, n (%)	67 (29)	28 (11)
Patients with SAEs, n (%)	9 (3.9)	7 (2.8)
Discontinuation due to AE, n (%)	7 (3.0)	4 (1.6)

AE = adverse event; n = number; Ona A = onabotulinumtoxinA; SAE = serious adverse event.
Source: Manufacturer's Pharmacoeconomic Report, Table 2, page 14.

2.2.3 Quality of life

Several measures for reporting patient outcomes, functioning, and quality of life were used in the PREEMPT studies. These include the Headache Impact Test (HIT-6), the Migraine-Specific Quality of Life Questionnaire (MSQ), the visual analogue scale (VAS) component of the EQ-5D (EQ-VAS), the Migraine Impact Questionnaire (MIQ), the Migraine Treatment Satisfaction Questionnaire (MTSQ), and the Illness Behavior Questionnaire (IBQ). The CDR Clinical Report provides a critique of the quality-of-life tools and data.

The manufacturer used the results from the MSQ to inform the utility values used in the model (see Section 2.2.7 for further information). Using the MSQ instead of the HIT-6 to inform the utility values appears appropriate based on Gillard et al.,[13] although a sensitivity analysis using the mapped HIT-6 results would also have been informative.

2.2.4 Costs

The manufacturer captured the treatment costs associated with onabotulinumtoxinA and BSC medications, as well as the costs of medical resource utilization.

2.2.5 Drug costs

The manufacturer submitted onabotulinumtoxinA at a cost of $3.57 per unit (U) in the submission, multiplying that figure by the average dose per 12 weeks in the PREEMPT trials (164 U) for a total drug cost of $585.48. OnabotulinumtoxinA is supplied as 50 U, 100 U, and 200 U vials, and according to the Product Monograph *"the use of one vial for more than one patient is not recommended because the product and diluent do not contain a preservative."* Thus, there will be wastage of the drug, which has not been taken into account. A more likely and conservative approach would have been to cost the full 200 U ($714).

BSC patients do not incur the cost of the drug. Since these patients have failed three or more oral prophylactic therapies, they are likely being monitored by their neurologist while continuing to use acute medications as needed. The use of acute medications and other resources is also dependent on the patients' health state. Use of concomitant medications was also included in the model.

2.2.6 Administration costs

The manufacturer stated that onabotulinumtoxinA is administered in office-based settings, with retreatment occurring every 12 weeks in accordance to the PREEMPT clinical protocol. The cost of the consultation was included in the model, with the same consultation used for both treatment arms. The manufacturer reported that in provinces other than Quebec and Alberta, the cost of the procedure is charged out-of-pocket to the patient (approximately $100) and thus is not relevant for the public payer perspective. However, should onabotulinumtoxinA be listed on drug plan formularies, the cost of the injection is likely to be listed as well given this is a medical procedure, thus increasing the cost of treatment.

The manufacturer assumed that BSC patients would visit the neurologist at least once every twelve weeks, with additional visits required depending on their health state. CDR clinical input has indicated that it is likely that using onabotulinumtoxinA will take an extra 15 to 20 minutes in addition to the original assessment time, and that therefore a different code may need to be used (see CDR reanalysis 1).

2.2.7 Event treatment costs

Hospitalization and emergency room (ER) visits were also included in the economic analysis, based upon the results of the International Burden of Migraine Study (IBMS). In this study, patients with chronic headache had significantly more hospitalizations and ER visits than patients with EM. The data that populated these parameters were determined from pooled data from the PREEMPT trials. Hospitalization and ER costs were determined from the Ontario Case Costing Initiative (OCCI) database and were reported to be $2,553 and $241 respectively. CDR clinical guidance has indicated that hospitalization and ER visits are not common for the treatment of CM in Canada, which, given the current shortage of beds in Canada's public hospitals, may indicate the potential overestimation of hospitalization and ER costs. However, one report of the IBM Study by Sanderson et al.[14] indicates that the small sample of patients from Canada had a higher rate of hospitalization and ER visits than patients from other countries participating in the study, which may make the manufacturer's approach conservative.

2.2.8 Concomitant medication costs

The use of triptan medications was also included in acute cases, although the Manufacturer's Pharmacoeconomic Report states that data from the PREEMPT studies reported that patients used simple analgesics (over-the-counter medications) more often than triptans (67.1% versus 63.3%); it is

unclear if these proportions are for the full population or the subpopulation. The cost of triptan use per attack was calculated by the manufacturer to be $16, based on the average weighted cost of currently listed triptans ($10.74) and the assumption that 50% of patients will have to be retreated. The manufacturer did not specify how it came to this calculation, although it appears that this costing is conservative.

Clinical data suggest that although no significant differences between groups in the frequency of acute headache pain medication consumption were seen in either study, there were significant differences in favour of onabotulinumtoxinA for triptan intake.[15]

2.2.9 Utilities

The manufacturer stated that the PREEMPT studies did not use any preference-based measures (e.g., EQ-5D or the Short-Form 36 Health Survey [SF-36]) but they did use disease-specific, health-related, quality-of-life measures (MSQ and HIT-6). The utilities for the model health states were derived by mapping the results from the MSQ to the EQ-5D. The mapping algorithm and methodology are presented in Gillard et al., 2012.[13] The HIT-6 results could also be mapped to the EQ-5D, although Gillard et al.[13] indicated that the MSQ appeared more appropriate. Although the manufacturer indicated that preference-based measures were not administered, the PREEMPT studies did use the VAS component of the EQ-5D. It appears as though data from the full PREEMPT-1 and PREEMPT-2 patient populations were used to determine the utility values.

The derived mapped utility values are presented in Table 4. The utility value for patients who discontinued treatment was calculated based on the weighted average utility at baseline in patients from both treatment arms. The health utility values for patients with zero to three headache attack days per 28-day period appear a little low, especially for patients with zero or one headache days per 28-day period. Higher utility values in the “0 to 3 headache days” health state would favour the onabotulinumtoxinA treatment arm.

TABLE 4: MODEL UTILITY VALUES FOR EACH HEALTH STATE

Headache Attack Days per 28 Days	Mapped Trial Utility Value	IBMS Utility Value
0 to 3 days	0.737	0.71
4 to 9 days	0.687	0.61
10 to 14 days	0.639	0.57
15 to 19 days	0.581	0.50
20 to 23 days	0.536	0.48
24 or more days	0.522	0.38
Discontinued	0.559	0.47

IBMS = International Burden of Migraine Study.
Source: Adapted from Manufacturer’s Pharmacoeconomic Report, Table 7, page 23, and Table 14, page 30 to 31.

The manufacturer also conducted sensitivity analyses using utility values derived directly from EQ-5D responses from the IBMS.[16] The EQ-5D responses had a United Kingdom weighting applied, and mean utility was calculated for each health state in the model. The IBMS utility values differed substantially from the mapped utility values used in the model (see Table 4 above). Alternatively, the manufacturer mapped treatment specific utilities from the PREEMPT trial. However, these values are non-monotonic and no rationale for using these values was presented, which may highlight some uncertainty between

the mapping of MSQ data to utilities and correspondence with the model structure as defined by the number of HDPM (see NICE guidance).[15]

2.2.10 Time horizon

The Manufacturer's Pharmacoeconomic Report stated that investigators in the PREEMPT clinical trials followed patients for a mean of 2.88 years. The manufacturer indicated there is evidence of continued efficacy associated with repeated injections of onabotulinumtoxinA up to approximately three years, and thus a time horizon of three years is appropriate. The base-case model uses a time horizon of 13 treatment cycles (156 weeks or approximately three years).

Mortality rates have not been factored into the model, as treatment is not expected to impact mortality.

CM is often a long-term condition. Depending upon the frequency of onabotulinumtoxinA use, a longer time horizon may have been more appropriate (see Discussion).

2.2.11 Discounting

Both outcomes and costs accrued beyond the first year of the model are discounted at a rate of 5%, as per the CADTH economic guidelines.[5] This is appropriate.

2.2.12 Validation

No formal validation was conducted. The clinical data are from the PREEMPT-1 and PREEMPT-2 trials, which suggests that they are valid, although utility values are mapped from disease-specific, quality-of-life measures to a multi-attribute utility instrument (e.g., EQ-5D) to determine utility values. The manufacturer also conducted a search of the literature, which found three relevant economic studies, one of which was Canadian. The three studies differed as compared with the submitted economic evaluation.

3. RESULTS

3.1 Manufacturer's Base Case

The manufacturer's primary analysis in the submission was an analysis of onabotulinumtoxinA versus BSC in the subpopulation of CM patients who had failed three or more prior oral prophylactic medications. In this subpopulation, treatment of patients with onabotulinumtoxinA resulted in a total cost of $8,151 per patient over the approximately three-year horizon, compared with $5,339 per patient with BSC. Patients receiving onabotulinumtoxinA had significantly fewer headache attack days and fewer days per year with headaches lasting for at least four hours compared with BSC. These clinical improvements translate to 1.75 QALYs gained with onabotulinumtoxinA versus 1.64 QALYs gained with BSC, leading to an incremental gain of 0.11 QALYs achieved with onabotulinumtoxinA therapy. This resulted in an incremental cost per QALY of $25,470 (Table 5).

TABLE 5: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE

	Total Costs	Incremental Cost of Ona A	Total QALYs	Incremental QALYs of Ona A	Incremental Cost per QALY
Ona A	$8,151	$2,812	1.745	0.110	$25,470
BSC	$5,339		1.635		

BSC = best supportive care; Ona A = onabotulinumtoxinA; QALY = quality-adjusted life-year.
Source: Manufacturer's Pharmacoeconomic Report, Table 18, page 37.

3.1.1 Scenario analysis

The manufacturer also undertook a scenario analysis of the full population. In this analysis, onabotulinumtoxinA resulted in an incremental cost per QALY of $28,940 versus BSC (Table 6).

TABLE 6: SUMMARY OF RESULTS OF THE MANUFACTURER'S SCENARIO ANALYSIS OF THE FULL POPULATION

	Total Costs	Incremental Cost of Ona A	Total QALYs	Incremental QALYs of Ona A	Incremental Cost per QALY
Ona A	$8,223	$3,101	1.771	0.107	$28,940
BSC	$5,122		1.664		

BSC = best supportive care; Ona A = onabotulinumtoxinA; QALY = quality-adjusted life-year.
Source: Manufacturer's Pharmacoeconomic Report, Table A3, page 54.

The manufacturer stated that a stopping rule was included in the model; patients who did not achieve a 30% reduction in headache days were discontinued from study treatment and received BSC for the remainder of the time horizon. These patients were indicated to have been included as "discontinued" patients in the model; however, patients who did not achieve the designated improvement were grouped with patients that discontinued for other reasons within the trial. It would have been more transparent had these patients been separated within the model.

Other scenario analyses that the manufacturer should have undertaken include:

- An analysis using data from PREEMPT-1 only (Study 191622-079)
- An analysis using data from PREEMPT-2 only (Study 191622-080)
- An analysis removing any patient that improved to the point of having fewer than 15 HDPM by week 12 and by week 24.

3.2 Summary of the Manufacturer's Sensitivity Analyses

3.2.1 One-way sensitivity analyses

The manufacturer conducted several one-way sensitivity analyses, based on either standard errors or assumptions of a 10% change from the base-case value for the input parameters, as well as alterations to the model assumptions. The manufacturer reported that the results were robust to changes in model assumptions, with the ICURs of most scenarios falling under the $50,000 per QALY willingness-to-pay threshold. The results ranged from $5,984 (societal perspective including work productivity) to $66,774 (reducing the time horizon to one year).

The frequency of migraine-related hospitalizations in the CM health states and utility values in the EM health states were found to be the most influential parameters.

The values used for the sensitivity analyses were generally appropriate.

3.2.2 Probabilistic sensitivity analysis

The manufacturer undertook a probabilistic sensitivity analysis (PSA) using 10,000 simulations. The PSA indicated that approximately 88% of iterations fell below a willingness-to-pay threshold of $50,000 per QALY.

The values used for the sensitivity analyses were generally appropriate.

3.3 CADTH Common Drug Review Analyses

The main areas of uncertainty identified by CDRs critique apply to the modelling of CM in both the full population and the subpopulation. The manufacturer made several assumptions in the structure of the model, which prevented CDR from conducting reanalyses of interest that would better inform reimbursement recommendations and decisions. The model appears to include patients who have improved from CM (≥ 15 HDPM) to EM (< 15 HDPM) and who continue to be treated with onabotulinumtoxinA. As onabotulinumtoxinA is indicated for CM only,[1] the manufacturer should have factored this stopping rule into its model. It appears as though discontinuation was modelled as an absorbing state; however, this is not transparent in the model, and these patients may have cycled back into the model at a later time point.

The trial data indicate that just 2% of onabotulinumtoxinA patients (14 out of 688 patients) who were in CM at week 12 remained in the group of patients that were in CM at week 24. The rest of the patients had either improved from CM (≥ 15 HDPM) to episode migraine (< 15 HDPM), or had discontinued (although six patients who had improved at week 12 to EM regressed back to CM at week 24). The open-label extension data indicate that fewer than 5% of patients had CM at week 36, at week 48, and at the end of the study. Between week 24 and the end of the study, 41 patients who had improved to EM (< 15 HDPM) transitioned back to CM. The study data indicate that from week 12 to the end of study, between 48% and 59% of study patients were no longer in the CM health state, and therefore would not be eligible to receive treatment with onabotulinumtoxinA. Thus, the inclusion of these patients for the duration of the model is not appropriate.

A model with either a stopping rule for patients who are no longer chronic migraineurs or a stopping rule that cycles these patients out of the model and back in with a recurrence of CM would have been more appropriate. CDR acknowledges that this would have been difficult to undertake given the available clinical data, and that any estimate would be conservative, as the proportion of patients transitioning back to CM is likely to be higher in patients who are not being treated with

onabotulinumtoxinA. However, given the high placebo effect in the trials, the true rate of relapse is not known.

CDR did note other assumptions that could be considered through reanalyses: the cost of physician visits for onabotulinumtoxinA, the cost of administration of onabotulinumtoxinA, and the cost of drug acquisition.

3.3.1 CADTH Common Drug Review reanalysis 1

CDR clinical guidance has indicated that onabotulinumtoxinA will take an extra 15 to 30 minutes to administer; thus, one of the following physician visit codes would have been more appropriate (A385 Limited consultation/A186 Repeat consultation)[17] for onabotulinumtoxinA, while the manufacturer specified code (A188) would remain appropriate for BSC (Table 7):

TABLE 7: CDR ANALYSES — REVISED ONABOTULINUMTOXINA CONSULTATION PRICE

	Manufacturer Base-Case ICUR (Based on $37.65 Consultation Fee)	CDR Reanalysis ICUR (Based on $84.95 Consultation Fee)
Full population	$28,940	$31,866
Subpopulation	$25,470	$28,130

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio.

3.3.2 CADTH Common Drug Review reanalysis 2

Should onabotulinumtoxinA be listed on drug plan formularies, the cost of the injection is likely to be listed by the plan as well given this is a medical procedure, thus increasing the cost of treatment. Ontario has a cost of injection for onabotulinumtoxinA of $120.00 (for other indications),[17] which may be at the upper limit of the cost as the costs of administration in other provinces have been reported to be between $57 and $75. Incorporating this upper range into the manufacturer's submission, the results are seen in Table 8.

TABLE 8: CDR ANALYSES — INCLUDE ADMINISTRATION COST

	Manufacturer Base-Case ICUR (Based on $0 Administration Cost)	CDR Reanalysis ICUR (Based on $120 Administration Cost)
Full population	$28,940	$36,364
Subpopulation	$25,470	$32,220

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio.

3.3.3 CADTH Common Drug Review reanalysis 3

Although the manufacturer based its analysis on the average number of units used in the trial (164 U), onabotulinumtoxinA is supplied as 50 U, 100 U, and 200 U vials. Vials cannot be reused, and thus, there will be associated wastage, which was not taken into account in the drug acquisition cost. The updated drug acquisition costs are shown in Table 9.

TABLE 9: CDR ANALYSES — DRUG ACQUISITION COST

	Manufacturer Base-Case ICUR ($585.48 Cost of Ona A)	CDR Reanalysis ICUR ($714 Cost of Ona A)
Full population	$28,940	$36,891
Subpopulation	$25,470	$32,699

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; Ona A = onabotulinumtoxinA.

3.3.4 CADTH Common Drug Review reanalysis 4

The proportion of patients who were hospitalized or who visited an ER may be lower than the proportion indicated in the manufacturer's submission. Table 10 shows the results of altering these proportions to 0% for all health states to denote a lower range. Table 11 also presents a range, based on information from the IBM Study (Sanderson et al.),[14] which uses values for the CM and EM health states of 0.52 and 0.35 respectively for ER admissions, and values of 0.22 and 0.16 respectively for hospitalizations. Although these values were for the full population, they have been used in the subpopulation analysis as well.

TABLE 10: CDR ANALYSES — EVENT TREATMENT COSTS: HOSPITALIZATION AND EMERGENCY ROOM VISITS

	Mfr. Base-Case Hosp. Values (EM | CM)		Mfr. Base-Case ER Values (EM | CM)		Mfr. Base-Case ICUR	Revised Hosp. and ER Values	CDR Reanalysis ICUR
Full population	0.03	0.09	0.10	0.41	$28,940	0.00	$34,939
Subpopulation					$25,470		$31,740

CDR = CADTH Common Drug Review; CM = chronic migraine (defined as ≥ 15 HDPM); EM = episodic migraine (defined as < 15 HDPM); ER = emergency room; Hosp = hospitalization; ICUR = incremental cost-utility ratio; Mfr = manufacturer.

TABLE 11: CDR ANALYSES – EVENT TREATMENT COSTS: HOSPITALIZATION AND EMERGENCY ROOM VISITS

	Mfr. Hosp. and ER Values	Mfr. Base-Case ICUR	Revised Hosp. Values (EM | CM)		Revised ER Values (EM | CM)		CDR Reanalysis ICUR
Full population	As per Table 10	$28,940	0.16	0.22	0.35	0.52	$29,828
Sub-population		$25,470					$26,398

CDR = CADTH Common Drug Review; CM = chronic migraine (defined as ≥ 15 HDPM); EM = episodic migraine (defined as < 15 HDPM); ER = emergency room; Hosp = hospitalization; ICUR = incremental cost-utility ratio; Mfr = manufacturer.

3.3.5 CADTH Common Drug Review reanalysis 5

Including the revised assumptions for CDR reanalyses 1, 2, and 3 within the economic evaluation simultaneously result in the ICURs identified in Table 12.

TABLE 12: CDR REANALYSIS — INCORPORATING REANALYSES 1, 2, AND 3

	Manufacturer's Base-Case ICUR	CDR Reanalysis ICUR
Full population	$28,940	$47,241
Subpopulation	$25,470	$42,110

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio.

3.3.6 Pricing analysis

Given the identified issues and uncertainties with the submitted structure for modelling CM, a price analysis was also undertaken to determine the price reduction required to achieve certain lower ICURs (Table 13).

TABLE 13: CDR ANALYSES – PRICE ANALYSES FOR ONABOTULINUMTOXINA

CDR Reanalysis 5	ICUR Versus BSC	Annual Cost of Ona A[a]	Basis
Full population	$47,241	$2,856	Submitted price[b]
	$25,155	$1,428	50% price reduction
	$10,136	$457	84% price reduction
Subpopulation	$42,110	$2,856	Submitted price[b]
	$25,241	$1,656	42% price reduction
	$10,381	$600	79% price reduction

BSC = best supportive care; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; Ona A = onabotulinumtoxinA.
[a] Based on four courses of injections.
[b] Manufacturer's submitted price of $3.57 per U; 31 to 39 injections of five U each (cost with wastage = $714), every 12 weeks.

To achieve an ICUR of $25,000, a 42% to 50% price reduction of onabotulinumtoxinA would be required.

4. DISCUSSION

The key limitation of the manufacturer's submitted economic evaluation is whether the submitted economic evaluation presents a good representation of the chronic nature of CM and its expected treatment. The key assumptions in the modelling of CM include interactions surrounding the patient population, health states, stopping rule, time horizon, and cycle length.

The CDR reanalysis section has already highlighted some of these issues. The model fails to adequately deal with EM patients — a population for which onabotulinumtoxinA is not indicated and which reflects a distinct clinical entity which differs from CM — by removing them from the model, or by cycling them out of the model upon transition to an EM health state and back into the model when they transition back to CM. Scenario analyses excluding these patients after the initial 12 weeks should have been undertaken, as well as at 24 weeks and at 36 weeks if the patients were stable in episodic disease at these time points (this appears to have been assessed by NICE). The exclusion of this stopping rule from the model may have an effect on the ICUR; however, given the effect of the included population and health states on other parameters such as the time horizon and cycle length, it is unclear what effect on the estimated ICUR this would have. The inclusion of EM patients also impacts on the health states used in the model which were based on the number of headache days. Three states in the submitted model were for patients with EM (0 to 3 HDPM, 4 to 9 HDPM, and 10 to 14 HDPM) may potentially be justified as the end cycle states for patients, given the different utility weights associated with the number of headache days; however, onabotulinumtoxinA has not been appropriately tested in this population (see onabotulinumtoxinA Product Monograph).[1]

With the alteration to the model structure, the potential for patients to be cycling out of the model when they transition to EM, and the potential for these patients to transition back into CM and re-enter the model, the three-year time horizon may not be appropriate. As CM, defined as ≥ 15 days per month

with headache lasting four hours a day or longer, is currently often a long-term condition (see CDR Clinical Report for patient characteristics in the trials), and as the manufacturer indicates that as onabotulinumtoxinA is a preventive therapy, continued treatment is needed for most patients to maintain treatment response and benefit, CDR assumes that a longer time horizon, where patients are expected continue on onabotulinumtoxinA indefinitely, may have been more appropriate. However, the long-term efficacy and safety in this population is largely unknown: "*onabotulinumtoxinA for chronic migraine has not been evaluated in clinical trials beyond 5 injection cycles*."[1] The cycle time used in the model was based on the frequency of administration of onabotulinumtoxinA. However, with the potential for patients to be cycling in and out of the model, and with the HC indication not stipulating that patients must have had 15 or more HDPM for more than three months (12 weeks) to be considered as having CM, a cycle time of four weeks may have been appropriate (especially as headache day data was captured for patients at four-weekly time points within the PREEMPT studies).

Table 14 provides a further summary of the limitations identified with the manufacturer's submission.

TABLE 14: KEY LIMITATIONS OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Parameter/Assumption	Issue	Impact
Health states/use in patients with EM	The model includes patients who improved to fewer than 15 HDPM, but were not cycled out of the model despite no longer being in the CM health state and thus ineligible for treatment with Ona A.	This inherently changes the structure of the model. A model in which patients cycle in and out depending upon their health state may have been more appropriate. Likely overestimates of costs and QALYs associated with both treatments.
Stopping rule: 30% improvement after 2 courses of injections; otherwise, drug is ceased	The clinical goal is to assist patients in returning to the EM health state. Clinical guidance uses a 50% reduction to measure response.[18-20] Separating non-responders from discontinued patients would have been more transparent to test other proportions (only 25%, 50%, and 75% improvements were assessed in the clinical trials).	Unknown applicability in clinical practice; potential for increased uncertainty in the results.
Patients who discontinue	It appears as though "discontinuation" is an absorbing state; however, this is not transparent in the economic model (see note below Figure 1). Impact on capturing the full clinical treatment pathway.	Lack of transparency does not allow CDR reanalysis. Potentially underestimates of costs and QALYs, as patients may be able to be cycled back into the treatment group.
Model time period	CM is a long-term condition, so depending on how Ona A is administered (given other identified limitations), it may have been more appropriate to model these patients over a lifetime time horizon.	Increasing the time horizon in the current model would indicate that the ICUR would decrease; however, in a revised model based on other identified limitations, it is uncertain what the estimated ICUR would resemble.

Parameter/Assumption	Issue	Impact
Cycle time	Given that the Health Canada indication does not state that the patient must have had 15 or more HDPM for 3 months before classification of CM (i.e., treatment start), a 4- week cycle time may have been more appropriate.	Based on the potential for patients to cycle in and out of the model from a positive stopping rule, a reanalysis for this limitation was not possible.
Manufacturer's requested listing (patients who have failed ≥ 3 prior oral prophylactic medications)	The submitted clinical data appear to be based on a post hoc analysis and a subgroup of this post hoc analysis.	Increases the uncertainty of the results.
Use of pooled data	Scenario analyses that presented the results of each study separately should have been undertaken, given the differences in results between the trials (see CDR Clinical Report).	Given the differences in the study results, the scenario analyses may have assisted with determining the stability of the results.
Resource costs	Clinical input has indicated that it will take an additional 15 to 30 minutes to administer onabotulinumtoxinA in patients during a visit to the physician. The model also does not take into account the potential training that physicians may need to administer the drug to patients.	Increases the cost of Ona A and the ICUR.
Stratification by health state	The data indicates there was not much of a change in the most severe health state (24 or more headache days per 28-day period).	ICUR in this population likely to be higher.

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.

4.1 Issues for Consideration

Other issues for consideration include:

- There is a need for treatments in patients with CM who have failed oral prophylactic therapies.
- OnabotulinumtoxinA has eight HC-approved indications, several of which have not been listed for use by public plans (only one of which was reviewed through CDR). Thus, there is a potential for onabotulinumtoxinA to be used for other indications. There is also the potential for onabotulinumtoxinA to be used outside the HC-specified indication for CM, as the manufacturer's real-world utilization data indicated that patients have received injections as frequently as every 33 days.
- There is also the potential issue of implementing stopping rules in clinical practice, as any improvement in this patient cohort may be seen as significant; if the treatment is working where others have failed, patients may not be inclined to stop treatment.
- Four other health technology assessment (HTA) bodies have considered onabotulinumtoxinA for this indication. The National Institute for Health and Care Excellence (NICE, United Kingdom) and the Pharmaceutical Benefits Advisory Committee (PBAC, Australia) have given onabotulinumtoxinA a positive recommendation, while the Scottish Medicines Consortium (SMC) and *l'Institut national d'excellence en santé et en services sociaux* (INESSS, Quebec) gave onabotulinumtoxinA a negative recommendation (see Appendix 5: Other Health Technology Assessment Findings).

4.2 Patient Input

Patient input was received from Headache Network Canada, which gathered information from surveys, seminars, and public forums from patients, as well as from caregivers. Their report indicated that patients with CM:

- experience pain that interrupts every facet of their life
- have difficulty accomplishing mentally challenging tasks
- deal with feelings of hopelessness and helplessness, guilt, stress, and depression
- may have diminished prospects with respect to schooling, employment, or having a family
- may have to miss work and cancel social and family activities and obligations when symptoms are severe
- deal with challenges such as a lack of specialists and physicians who are adequately trained to treat CM, the comorbid conditions that make diagnosis difficult, and the expensive out-of-pocket costs of treatment

Caregivers and family report that living with, or caring for, someone with CM takes a lot of patience. It also has a marked effect on their social life. The manufacturer did undertake a partial societal perspective as well, including lost work time, which was included in the reporting of the manufacturer's sensitivity analyses.

Respondents cited a 50% reduction in headache days as the marker of treatment efficacy. The manufacturer used 30% in its economic evaluation, although the PREEMPT studies collected information based on 25%, 50%, 75%, and 100% reductions. No respondents reported that undergoing therapy with injections was a deterrent to receiving treatment with onabotulinumtoxinA. The economic model did not address AEs such as injection pain; however, given this response, this may be justified.

5. CONCLUSIONS

The manufacturer's base case may underestimate the ICUR for onabotulinumtoxinA. Given the limitations of the structure of the submitted model with regard to modelling CM, there is considerable uncertainty with the submitted and CDR-revised cost-effectiveness ratios. Within the confines of the submitted model structure, CDR noted several costing errors which when reassessed increased the ICUR to between $42,000 and $47,000 per QALY.

APPENDIX 1: COST COMPARISON TABLE

Clinical experts have deemed the comparators presented in Table 15 to be appropriate. 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.

TABLE 15: COST COMPARISON TABLE FOR DRUGS USED FOR PROPHYLAXIS OF CHRONIC MIGRAINE

Drug	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Onabotulinumtoxin A (Botox)	50 U 100 U 200 U	Inj 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 Migraine Prophylaxis						
Pizotyline/pizotifen (Sandomigran)	0.5 mg 1.0 mg	Tab	0.3972 0.6726	1.5 mg to 6 mg per day	1.07 to 4.04	390 to 1,473
Topiramate (generics)	25 mg 100 mg 200 mg	Tab	0.3128 0.5929 0.8854	50 mg twice daily	1.25	457
Flunarizine[c,d] (generics)	5 mg	Cap	0.7204	10 mg per day	0.72	236
Comparators Not Currently Indicated for Migraine Prophylaxis						
Anti-epileptics						
Divalproex *Sodium*[c,d] *(generics)*	125 mg 250 mg 500 mg	Ent Tab	0.0724 0.1301 0.2604	500 mg to 1,500 mg per day	0.26 to 0.78	95 to 285
Valproic Acid[c,d] (generics)	250 mg 500 mg	Cap Ent Cap	0.1366 0.4125	500 mg to 1,500 mg per day	0.27 to 1.24	100 to 452
Gabapentin[c,d] (generics)	100 mg 300 mg 400 mg	Cap	0.1060 0.2578 0.3072	1,200 mg to 1,800 mg per day	0.92 to 1.55	366 to 565
Antidepressants						
Amitriptyline[c,d] (Elavil)	10 mg 25 mg 50 mg	Tab	0.0664 0.1211 0.2347	10 mg to 100 mg per day	0.07 to 0.47	24 to 171
Doxepin[d] (generics)	10 mg 25 mg 50 mg 75 mg 100 mg 150 mg	Cap	0.1889 0.2140 0.3971 0.3916 0.5160 0.7820	25 mg to 100 mg per day	0.21 to 0.52	78 to 188
Nortriptyline[d] (generic)	10 mg 25 mg	Cap	0.0500 0.1011	20 mg to 150 mg per day	0.10 to 0.61	36 to 223
Venlafaxine[c,d] (generics)	37.5 mg 75 mg 150 mg	ER Cap	0.1643 0.3285 0.3469	150 mg per day	0.35	127

Drug	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Antihypertensives						
Atenolol[d] (generics)	50 mg 100 mg	Tab	0.1437 0.2362	100 mg to 200 mg per day	0.24 to 0.47	86 to 172
Propranolol[c,d] (generics)	10 mg 20 mg 40 mg 80 mg 120 mg	Tab	0.0172 0.0277 0.0306 0.0509 0.3091	80 mg to 160 mg per day	0.05 to 0.10	19 to 37
Nadolol[c,d] (generics)	40 mg 80 mg 160 mg	Tab	0.2465 0.3515 1.2046	80 mg to 160 mg per day	0.35 to 0.70	128 to 257
Metoprolol[c,d] (generics)	50 mg 100 mg	Tab	0.0624 0.1361	100 mg to 200 mg per day	0.14 to 0.27	50 to 99
	100 mg 200 mg	SR Tab	0.1415 0.2568		0.14 to 0.26	52 to 94
Verapamil[c,d] (generics)	80 mg 120 mg	Tab	0.2735 0.4250	80 mg, three to four times daily	0.82 to 1.09	299 to 399
	120 mg 180 mg 240 mg	SR Tab	0.5078[e] 0.5204 0.5075	240 mg to 320 mg per day	0.51 to 1.04	185 to 380
Candesartan[c] (generics)	4 mg 8 mg 16 mg 32 mg	Tab	0.1700 0.2850 0.2850 0.2932	16 mg per day	0.28	104
Lisinopril[c] (generics)	5 mg 10 mg 20 mg	Tab	0.1347 0.1619 0.1945	20 mg per day	0.19	71
Antimanic						
Lithium Carbonate[d] (generics)	150 mg 300 mg	Cap	0.0422 0.0443	300 mg, three times daily	0.13	49

cap = capsule; CPhA = Canadian Pharmacists Association; ent = enteric; ER = extended release; inj = injection; SR = sustained release; tab = tablet.

[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." Thus, wastage has been included for onabotulinumtoxinA in Table 15.

[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 four or five courses of injections in a year).

[c] Source: 2012 *Canadian Headache Society Guideline for Migraine Prophylaxis* (http://headachenetwork.ca/wp-content/uploads/CanadianHeadacheSocietyGuidelineforMigraineProphylaxis.pdf).

[d] Source: CPhA Therapeutic Choices: Medications for Migraine Prophylaxis (Accessed Nov 7, 2013).

[e] Source: Saskatchewan Formulary (November 2013).

Pricing Source: Ontario Drug Benefit Formulary (November 2013) unless otherwise indicated.

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 16: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS ONABOTULINUMTOXINA RELATIVE TO BEST SUPPORTIVE CARE?

Ona A Versus BSC	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)				X		
Drug treatment costs alone					X	
Clinical Outcomes		X				
Quality of Life		X				
Incremental CE Ratio or Net Benefit Calculation	$25,470 per QALY (restricted population) $28,940 per QALY (full population)					

BSC = best supportive care; CE = cost-effectiveness; NA = not applicable; Ona A = onabotulinumtoxinA.
Note: Table 16 is based on both results from the manufacturer.

CADTH Common Drug Review (CDR) reanalyses could not provide an accurate estimate of the incremental cost-utility ratio (ICUR), given the issues around the model assumptions and uncertainties in the clinical data.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 17: SUBMISSION QUALITY

	Yes/Good	Somewhat/ Average	No/Poor
Are the methods and analysis clear and transparent?		X	
Comments	The model was generally transparent; however, there was some uncertainty around the negative stopping rule.		
Was the material included (content) sufficient?		X	
Comments	As identified in the limitations, the indication and results of the clinical trial suggested that a different model structure may have been more appropriate, for which further information would be required.		
Was the submission well organized and was information easy to locate?		X	
Comments	As previously stated, while the model was generally transparent, some aspects within the model (such as the negative stopping rule) were difficult to pinpoint. There was also some uncertainty with regard to how certain fields within the model were being used (posterior dirichlet distributions).		

TABLE 18: AUTHOR INFORMATION

Authors	Affiliations		
Laurie Kan	Allergan Inc.		
	Yes	**No**	**Uncertain**
Authors signed a letter indicating agreement with entire document.	X		
Authors had independent control over the methods and the right to publish the analysis.	X		

APPENDIX 4: SUMMARY OF CLINICAL INFORMATION

Full Population

The submission relied upon pooled patient-level data from the two phase 3 clinical studies to estimate the clinical efficacy of onabotulinumtoxinA in the first 24 months. The primary outcome PREEMPT-1 was the frequency of headache episodes[a] per 28-day period, which was revised in PREEMPT-2 to the frequency of headache days[b] per 28-day period. The results from the intention-to-treat (ITT) population indicated large mean reductions in headache days per 28-day period for both onabotulinumtoxinA and placebo at week 24 (8.4 days and 6.6 days respectively), with statistically significant between-group differences favouring onabotulinumtoxinA.[12]

Clinical guidelines suggest a 30% to 50% reduction in headache days is a clinically meaningful reduction.[18-20] The proportions of patients achieving this mark for the full HC indication were not reported. It is unclear how these proportions were determined, as the results of the studies reported the reduction in headache days as being either 25% or 50%. CDR clinical input indicated that reducing the number of headache days so that the patient is no longer classed as having CM would be at least as appropriate, considering onabotulinumtoxinA has only shown potentially favourable results in the CM population. Patients transitioning from one health state to another are of pivotal importance to the model. The tables below represent an abbreviated transition matrix of ITT patients from the pooled PREEMPT-1 and PREEMPT-2 trials who transitioned between states between weeks 0 and 12 (Table 19), and weeks 12 and 24 (Table 20) in the onabotulinumtoxinA (Botox) group.

TABLE 19: SUMMARY OF HEADACHE DAYS FOR BOTOX PATIENTS FROM THE POOLED PREEMPT ITT DATA (BASELINE TO WEEK 12)

		At 12 Weeks					
		< 15 Days/ Month	15 to 19 Days/ Month	20 to 23 Days/ Month	24+ Days/ Month	Discontinued	Total
Baseline	< 15 days/month	0	0	0	0	0	0
	15 to 19 days/month	274	36	19	4	23	356
	20 to 23 days/month	95	48	32	14	9	198
	24+ days/month	36	22	26	41	6	131
	Discontinued	0	0	0	0	3	3
	Total	405	106	77	59	41	688

ITT = intention-to-treat.
Source: Adapted from Manufacturer's Economic Model, sheet "Transitions_Botox."

[a] A headache episode was defined as consisting of four or more hours of continuous headache as reported per electronic diary.
[b] A headache day was defined as a day when a patient reported four or more continuous hours of headache in the electronic diary.

TABLE 20: SUMMARY OF HEADACHE DAYS FOR BOTOX PATIENTS FROM THE POOLED PREEMPT ITT DATA (WEEK 12 TO WEEK 24)

		At 24 Weeks					
		< 15 Days/ Month	15 to 19 Days/ Month	20 to 23 Days/ Month	24+ Days/ Month	Discontinued	Total
At 12 Weeks	< 15 days/month	309	6	0	0	90	405
	15 to 19 days/month	40	6	0	0	60	106
	20 to 23 days/month	21	6	0	0	50	77
	24+ days/month	2	2	0	0	55	59
	Discontinued	0	0	0	0	41	41
	Total	372	20	0	0	296	688

ITT = intention-to-treat.
Source: Adapted from Manufacturer's Economic Model, sheet "Transitions_Botox."

Subpopulation

The pooled PREEMPT study subpopulation (failed three or more oral prophylactic therapies) results reported in the Manufacturer's Pharmacoeconomic Report[4] indicate that the patients treated with onabotulinumtoxinA experienced a greater mean reduction from baseline (7.4 days) in the number of headache days per 28-day period compared with patients receiving placebo (4.7 days).

Clinical guidelines suggest a 30% to 50% reduction in headache days is a clinically meaningful reduction.[18-20] The pooled results for the subpopulation in the PREEMPT studies indicate that 57% of onabotulinumtoxinA patients achieved a 30% reduction in headache days at 24 weeks compared with 46% of placebo patients.

Tables 21 and 22 represent transition matrices for the requested subpopulation of patients in the onabotulinumtoxinA (Botox) group from the PREEMPT trials, between weeks 0 and 12 (Table 21) and between weeks 12 and 24 (Table 22).

TABLE 21: SUMMARY OF HEADACHE DAYS FOR BOTOX PATIENTS FROM THE POOLED PREEMPT SUBPOPULATION DATA (BASELINE TO WEEK 12)

		At 12 Weeks					
		< 15 Days/ Month	15 to 19 Days/ Month	20 to 23 Days/ Month	24+ Days/ Month	Discontinued	Total
Baseline	< 15 days/month	0	0	0	0	0	0
	15 to 19 days/month	82	16	10	1	6	115
	20 to 23 days/month	33	17	11	10	4	75
	24+ days/month	7	5	10	16	3	41
	Discontinued	0	0	0	0	0	0
	Total	122	38	31	27	13	231

Source: Adapted from Manufacturer's Economic Model, sheet "Transitions_Botox."

TABLE 22: SUMMARY OF HEADACHE DAYS FOR BOTOX PATIENTS FROM THE POOLED PREEMPT SUBPOPULATION DATA (WEEK 12 TO WEEK 24)

		At 24 Weeks					
		< 15 Days/ Month	15 to 19 Days/ Month	20 to 23 Days/ Month	24+ Days/ Month	Discontinued	Total
At 12 Weeks	< 15 days/month	98	1	0	0	23	122
	15 to 19 days/month	10	1	0	0	27	38
	20 to 23 days/month	7	3	0	0	21	31
	24+ days/month	1	1	0	0	25	27
	Discontinued	0	0	0	0	13	13
	Total	116	6	0	0	109	231

Source: Adapted from Manufacturer's Economic Model, sheet "Transitions_Botox."

APPENDIX 5: OTHER HEALTH TECHNOLOGY ASSESSMENT FINDINGS

Four health technology assessment (HTA) bodies have published recommendations regarding onabotulinumtoxinA for CM: National Institute for Health and Care Excellence (United Kingdom); Scottish Medicines Consortium (Scotland), Pharmaceutical Benefits Advisory Committee (Australia), and L'Institut national d'excellence en santé et en services sociaux (INESSS; Quebec). Summaries of these recommendations are provided below. (Note: A summary of the INESSS recommendations has not been included.)

TABLE 23: OTHER HEALTH TECHNOLOGY ASSESSMENT ORGANIZATIONS' FINDINGS

	NICE	SMC	PBAC (Initial and Subsequent Submissions)
Drug	Botulinum toxin type A, 31 to 39 injections of 5 units every 12 weeks		Botulinum toxin type A purified neurotoxin complex, dose not specified.
Price	£276.40 per vial (assuming 5 sets of injections per year = £1,382)	£1,198 per year (based on 5 sets of injections)	Not reported
Treatment	Reported as Botulinum toxin type A (although, clinical data were from PREEMPT studies in which patients in both arms used concomitant acute medications)		
Comparator	Placebo	BSC (which includes combinations of first-line oral prophylactics, off-label prophylactics, GON blocks and in some cases acute migraine medications only), but SMC considered placebo more appropriate.	BSC (use of acute headache pain medications as required). PBAC considered other oral prophylactic treatments to be more appropriate, but agreed BSC was appropriate in subsequent applications.
Population Modelled	Adults with CM (whose condition has failed to respond to three or more prior pharmacological prophylactic therapies)	Adults with CM who had previously failed on oral prophylactic therapy due to side effects or lack of efficacy.	Adult patients with CM who failed 2 or more [initial] and 3 or more [subsequent] prior prophylactic treatments.
Time Horizon	2 years		5 years
Discount Rate	3.5% p.a. on both costs and outcomes	Not reported	
Type of Model	Markov model with 6 defined health states	CUA (model type not reported)	Markov model over six health states. Resubmission presented a model with three health states in a SA.
Key Outcomes	QALYs		
Results	Base case: £6,083 per QALY. Full population: £5,828 per QALY. SA: Majority of NICE	Base case: £17,436 per QALY. SA: results sensitive to changes in utility values and time horizon (increase ICUR to	Base case: $15,000 to $45,000 per QALY.[a] However, PBAC noted this may not represent the true

	NICE	SMC	PBAC (Initial and Subsequent Submissions)
	reanalyses found the ICUR to be between £11,267 and £20,324 per QALY. A revised economic model was submitted where NICE found the ICUR to be closer to £18,000.	£24,000 per QALY).	cost-effectiveness of botulinum toxin treatment in clinical practice, given a number of issues with the economic evaluation.
Sources of Uncertainty	Concern about whether blinding was maintained in studies, use of discontinuation in the model, application of stopping rules in practice	Resource use, clinical data (post hoc analysis), continued efficacy of treatment, other costs not considered (training).	Transitional probabilities, time horizon, application of stopping rules in practice, utility values, extrapolation of the incremental treatment effect in the absence of supportive evidence.
CDR Assessment	The model structure submitted to CDR appears to have been similar to those submitted to other HTA agencies.		

CDR = CADTH Common Drug Review; CUA = cost-utility analysis; GON = greater occipital nerve; HTA = health technology assessment; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; NICE = National Institute for Health and Care Excellence; p.a. = per annum; PBAC = Pharmaceutical Benefits Advisory Committee (Australia); QALY = quality-adjusted life-year; SA = sensitivity analysis; SMC = Scottish Medicines Consortium.
[a] Australia only reports ranges for ICERs.
Note: Other European countries also reimburse eplerenone for its new indication.

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