CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

ONABOTULINUMTOXINA (BOTOX — ALLERGAN INC.)
Indication: Chronic Migraine

RECOMMENDATION
The CADTH Canadian Drug Expert Committee recommends that onabotulinumtoxinA (OnaA) be reimbursed for the prophylaxis of headaches in adults with chronic migraine, if the following conditions are met.

Conditions for Reimbursement

Initiation criteria
1. The patient has a confirmed diagnosis of chronic migraine according to the International Headache Society criteria, defined as headaches on at least 15 days per month for more than three months of which at least eight days per month are with migraine.
2. The patient has already experienced an inadequate response, intolerance, or contraindication to at least three oral prophylactic migraine medications.
3. The physician must provide the number of headache days per month and the score obtained on the Headache Impact Test (HIT-6) at the time of initial request for reimbursement.
4. The maximum duration of initial authorization is nine months.

Renewal criteria
1. The physician must provide proof of beneficial clinical effect when requesting continuation of reimbursement, defined as:
   1.1. A reduction of at least 50% in the number of headache days per month compared with baseline, or
   1.2. A reduction of at least 30% in the number of headache days per month and an improvement of at least five points in the HIT-6 score, compared with baseline.
2. The maximum duration of subsequent authorizations following the initial authorization is 12 months.

Prescribing conditions
1. Administration should only be carried out by physicians with the appropriate qualifications and experience with the proper administration and therapeutic use of OnaA for migraine headaches.

Pricing conditions
Reduction in price.

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ONABOTULINUMTOXINA (BOTOX — ALLERGAN INC.)

Indication: Chronic Migraine

This recommendation supersedes the CADTH Canadian Drug Expert Committee (CDEC) recommendation for this drug and the indication dated May 28, 2014.

Recommendation

CDEC recommends that onabotulinumtoxinA (OnaA) be reimbursed for the prophylaxis of headaches in adults with chronic migraine, if the following conditions are met.

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2. The maximum duration of subsequent authorizations following the initial authorization is 12 months.

Prescribing conditions

1. Administration should only be carried out by physicians with the appropriate qualifications and experience with the proper administration and therapeutic use of OnaA for migraine headaches.

Pricing conditions

1. Reduction in price.

Reasons for the Recommendation

1. Patient groups identified an unmet need for effective and well-tolerated prophylactic medications for chronic migraine in patients who have tried and failed oral prophylactic medications. CDEC concluded that OnaA could meet this need. Two randomized controlled trials (RCTs) (PREEMPT-1 and PREEMPT-2) demonstrated that OnaA was statistically superior to placebo for reducing the number of headache days and migraine/probable migraine days in patients with chronic migraine (range of –1.4 to –2.3 headache days per 28-day period and [redacted] migraine/probable migraine per 28-day period). However, the clinical significance of these results is uncertain. The magnitude of the treatment effect appears to be larger and potentially more relevant to the subpopulation of patients who received at least three prior prophylactic medications (approximately [redacted] fewer days per month). Based on statistically significant differences versus placebo, OnaA treatment appears to improve health-related quality of life (HRQoL) and decrease the intensity of migraines, using the HIT-6 assessment tool. CDEC considered the differences in HIT-6 scores to be clinically meaningful for some patients with chronic migraine. Therefore, OnaA may provide an additional prophylactic option for the subpopulation who have few other treatment options.

2. At the recommended dose of 155 Allergan units to 195 units every 12 weeks, the cost of OnaA is $714 per treatment (including wastage). The cost-utility model provided for the resubmission was focused on first-line prophylaxis of adults with chronic migraine, and CADTH estimated that the incremental cost-utility ratio (ICUR) of OnaA compared with best supportive care (BSC) in this population is approximately $135,000 per quality-adjusted life-year (QALY); however, there is uncertainty in this estimate because of limitations with the model structure and comparative effectiveness data that could not be adequately addressed. The

manufacturer estimated that the ICUR in patients who had failed several oral prophylactic medications for migraine was $25,000 per QALY; however, this estimate does not take into account the relevant reanalyses applied by CADTH to the full population in the base case and likely underestimates the ICUR for OnaA. Therefore, the cost-effectiveness is uncertain in adults with chronic migraine who have failed prior oral prophylactic medications, but would likely be acceptable with an appropriate price reduction.

Implementation Considerations

1. Inadequate response to oral prophylactic therapies is defined as less than a 30% reduction in frequency of headache days to an adequate dose and duration of at least three prophylactic medications, where at least two must be of a different class.
2. Oral prophylactic therapies to be considered include:
    - Beta blockers
    - Tricyclic antidepressants
    - Verapamil or flunarizine
    - Sodium valproate (or divalproex sodium)
    - Topiramate
    - Gabapentin
3. A list of previously tried oral prophylactic medications, including doses, and duration and reasons for discontinuance, should be provided by the requesting physician.
4. Contraindication or intolerable adverse effects necessitating discontinuation of oral prophylactic therapy will be considered for one of the three drugs only.
5. Confirmation of specific training in the management of headache should be provided by the physician applying for reimbursement of treatment with OnaA.

Discussion Points

- Chronic migraine is a common and debilitating headache disorder that may lead to poor quality of life, social isolation, and an inability to participate in daily activities. CDEC discussed patient and clinician input that current prophylactic medications do not benefit everyone with chronic migraine and have adverse effects that may make them difficult to take leading to poor adherence to regimens and non-achievement of desired outcomes.
- CDEC reviewed evidence regarding the minimally clinically important difference (MCID) for headache and migraine frequency for chronic migraine. Several important methodological limitations preclude any conclusion for the MCID. Therefore, the therapeutic value of the approximately one to two day absolute difference in headache and migraine days between OnaA and placebo in the overall analysis population of the PREEMPT studies is uncertain.
- Given the uncertainty in the clinical relevance of the results of the primary analysis in the PREEMPT studies, CDEC identified the subgroup of patients who had a prior history of at least three oral prophylactic medications as appearing to be more likely to benefit from OnaA. CDEC noted several limitations with the subgroup analyses — such as the post-hoc nature of the analyses and lack of a clear definition for the subgroup — that lead to uncertainty in the validity of the results and uncertainty in the cost-effectiveness estimates.
- An evidence gap identified in the 2014 CDEC recommendation was the absence of data on the comparative effects of OnaA, relative to currently available drugs. The FORWARD study evaluated the efficacy and safety of OnaA versus topiramate in adult patients with chronic migraine. However, there are important limitations of the FORWARD study, including the open-label design and the high rate of withdrawal (80%) among patients randomized to topiramate. These limitations may have biased the trial outcome in favour of OnaA. Furthermore, the results were very sensitive to assumptions about headache frequency among those who discontinued topiramate. Together, these limitations meant the treatment effect estimate of OnaA's therapeutic value was associated with considerable uncertainty.
- There were more adverse events and serious adverse events associated with OnaA treatment than placebo from the PREEMPT trials, notably eyelid ptosis, neck pain, and muscular weakness, and pain. However, no unexpected adverse events were observed and the incidence of adverse events was generally of low concern.
- CDEC discussed the results of a small pilot RCT (N = 52), Study 545, that was conducted to investigate the utility of a new instrument developed to measure the impact of chronic migraine on daily activities and patient-treatment benefit for drugs developed to treat chronic migraine. Study 545 was not intended to provide robust evidence of efficacy and safety of OnaA.

- New data from four single-group interventional studies (COMPEL, REPOSE, Negro et al. 2015, and Negro et al. 2016) suggested that OnaA reduces the frequency of chronic migraine days. However, because these studies were limited by the lack of a comparator group and had high study discontinuation rates (COMPEL, 47.9% and REPOSE, 79.8%), CDEC considered the results too uncertain to make conclusions regarding the therapeutic value of OnaA.
- Data are lacking from high-quality studies to estimate the effect of OnaA on outcomes important to patients, including functionality, regaining active work and personal life roles, reducing analgesic consumption, particularly opiates, and reducing frequency of emergency department visits.
- CDEC discussed the inclusion of patients with chronic migraine and medication overuse headache in the PREEMPT-1 and PREEMPT-2 trials was unlikely an important modifier of the observed effects of OnaA.

Background

This resubmission for OnaA is for the Health Canada-approved indication for the prophylaxis of headaches in adults with chronic migraine (≥ 15 days per month with headache lasting four hours a day or longer).

OnaA is a purified neurotoxin complex produced from the fermentation of *Clostridium botulinum* type A. It is also indicated for the treatment of blepharospasm, strabismus, cervical dystonia (spasmodic torticollis), focal spasticity, equinus foot, bladder dysfunction, overactive bladder, and primary hyperhidrosis of the axillae.

The recommended dosage of OnaA for the prophylaxis of chronic migraine is 155 units administered intramuscularly (IM) (0.1 mL injection [five units] to each of 31 sites on the head and neck). Additional injections may be administered for a total maximum dose of 195 units (39 sites). The recommended retreatment schedule is every 12 weeks.

Submission History

OnaA was previously reviewed in 2014 for the same indication: the prophylaxis of headaches in adults with chronic migraine (≥ 15 days per month with headache lasting four hours a day or longer). OnaA received a CDEC recommendation of “not be listed” (see Notice of CDEC Final Recommendation, May 28, 2014).

The original CADTH Common Drug Review (CDR) systematic review of OnaA included two multi-centre, double-blind, parallel-group, randomized, placebo-controlled, phase III superiority trials. PREEMPT-1 (N = 679) and PREEMPT-2 (N = 705) enrolled adult patients who had experienced 15 or more headache days during a four-week period. Patients were randomized to receive 155 units of OnaA or placebo administered intramuscularly every 12 weeks. The duration of the double-blind treatment phase in both studies was 24 weeks.

Key reasons for the CDEC recommendation included the limitations with the design of the two pivotal trials (PREEMPT-1 and PREEMPT-2), and the absolute difference between the OnaA and placebo groups was relatively small for this chronic condition.

In addition, CDEC identified the following areas as constituting evidence gaps:

- Magnitude and clinical significance of OnaA effect in improving HRQoL and reducing the number of headache days and migraine/probable migraine days in patients with chronic migraine.
- Efficacy and safety in patients with or without medication overuse headache.
- Inadequate data regarding the long-term safety and efficacy of OnaA used for the prophylaxis of headaches in adults with chronic migraine.

The manufacturer resubmitted OnaA with additional data and information from studies that were not available at the time of the original submission to CDR, in order to address the evidence gaps identified by CDEC with the 2014 review. The manufacturer provided two RCTs, one of which compared OnaA with topiramate. The manufacturer also provided several articles that presented results from studies on MCIDs for the outcomes that were deemed important for patients with chronic migraine. Also, new evidence was provided to support the efficacy of OnaA in patients with chronic migraine and with or without medication overuse headache

from studies that have been published since the original CDR clinical review was conducted. Finally, the manufacturer provided prospective and retrospective non-randomized trials that have been published on the long-term safety and efficacy of OnaA when used as preventive treatment of chronic migraine.

Summary of Evidence Considered by CDEC

CDEC considered the following information prepared by CDR: evidence from the original CDR review on OnaA, an updated systematic review of clinical studies of OnaA identified since the original review, one indirect treatment comparison (ITC) identified from the literature search, articles that present results for the MCIDs for the outcomes that were deemed important for patients with chronic migraine, and a critique of the manufacturer's pharmacoeconomic evaluation. CDEC also considered input from a clinical expert who has experience in treating patients with chronic migraine, as well as patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

One patient group, Migraine Canada, provided input for this submission. Patient perspectives were obtained from online surveys that included 251 patients suffering from chronic migraine. The following is a summary of key input from the perspective of the patient group:

- Migraines have a significant impact on patients' lives. During attacks, the ability to accomplish tasks, work, and interact with others is compromised. Cognition is affected, with slowed thinking, lack of focus, and difficulty in reading and speaking. Of the survey respondents, 45% indicated having been disabled as a result of migraines, unable to work, and dependent on others for many activities of daily living.
- Patients often try multiple medications with no success and seek alternative therapies.
- Patients often experience side effects from therapies including sleepiness, fatigue, weight gain, gastrointestinal upset, depression, anxiety or mood difficulties, dizziness, cognitive problems, low blood pressure, fainting, and exercise intolerance. These are frequently problematic enough to lead to discontinuation of medication.
- For patients, the most important aspect of a treatment is efficacy, followed secondly by safety and tolerability.
- While patients do not expect a cure, they do expect that treatments will reduce the frequency of migraines, reduce dependence on medications, and improve HRQoL.

Clinical Trials

The original CDR systematic review of OnaA included the PREEMPT-1 and PREEMPT-2 RCTs. Key limitations of the studies included the lack of efficacy and safety comparisons between OnaA and standard prophylactic chronic migraine treatments, the difficulty in maintaining blinding, and the baseline imbalance in some patient characteristics between the OnaA and placebo groups in study PREEMPT-1. The studies were 24 weeks in duration and therefore did not provide blinded, comparative, longer-term efficacy and safety data on OnaA. The total study duration (double-blind plus open-label phases) was relatively short (one year) for a chronic condition for both studies. Adjustments for type I error were done for some, but not all, secondary efficacy outcomes.

The updated systematic review included two RCTs (FORWARD and Study 545) and four single-arm trials (COMPEL, REPOSE, Negro et al. 2015, and Negro et al. 2016). All trials included adult patients with chronic migraine, with Negro et al. 2015, and Negro et al. 2016 including patients with chronic migraine and medication overuse headache.

The FORWARD study (N = 282) was a prospective, multicenter, randomized, open-label, parallel-group, study that evaluated the efficacy, safety, and tolerability of OnaA 155 units administered approximately every 12 weeks IM as 31 fixed-site, fixed-dose injections across seven specifically-defined head and neck muscle areas, versus topiramate administered orally at doses up to 100 mg/day (minimum 50 mg/day), until week 36 or early discontinuation. Study 545 (N = 52), was a multicenter, randomized, double-blind trial that compared OnaA 155 units with placebo during a 24-week period. COMPEL study (N = 716), REPOSE study (N = 641), Negro et al. 2015 (N = 155), and Negro et al. 2016 (N = 172) evaluated the efficacy and safety of OnaA (155 units in COMPEL study, and Negro et al. 2015, 155 units or 195 units in REPOSE study, and 195 units in Negro et al. 2016) for up to a two-year period.

The main limitations of the FORWARD trial were its open-label design and the high discontinuation rate in the topiramate group (80.3% versus 14.3% who discontinued OnaA treatment). Being aware of treatment allocation could have biased the subjective outcome measures (including adverse events [AEs] and HRQoL). The high discontinuation rate in the topiramate group, where. In Study 545, the study was not designed as an efficacy study per se, and no formal sample size calculation was conducted. Therefore, Study 545 was not intended to provide robust evidence of efficacy and safety of OnaA.

The COMPEL, REPOSE, Negro et al. 2015 and Negro et al. 2016 studies were single-arm studies. There is a risk of bias with outcome measurement in single-arm studies as patients and providers are aware of their assigned intervention and the lack of a comparison group. The discontinuation rate was high in COMPEL (47.9%) and REPOSE (79.8%). Negro et al. 2015 and Negro et al. 2016 were studies conducted independent of the manufacturer, and as such, in-depth study reports were not available to the manufacturer or CADTH.

Outcomes

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

- Improvement in headache/migraine days, reported as:
  - per cent reductions in headache days per a 28-day period
  - frequency of headache days per a 28-day period
  - per cent reduction in migraine/probable migraine days per a 28-day period
  - frequency of migraine/probable migraine days per a 28-day period
  - frequency of moderate/severe headache days per a 28-day period
  - total cumulative hours of headache occurring on headache days per a 28-day period.
- Improvement in headache/migraine episodes — reported as the frequency of headache episodes per a 28-day period and the frequency of migraine/probable migraine episodes per a 28-day period.
- Migraine-Specific Quality of Life Questionnaire (MSQ) — a self-reported disease-specific instrument that assesses the impact of migraine on a patient's HRQoL. The questionnaire comprises three domains: role function restrictive (RFR), role function preventive (RFP), and emotional function (EF). For each domain, scores range from 0 to 100. A higher score indicates a better HRQoL. MSQ can also be scored in the reverse fashion, with a lower score indicating higher function. In COMPEL and REPOSE, higher scores indicated better HRQoL. The reverse scoring method was used in Study 545, PREEMPT-1, and PREEMPT-2, where a negative number change from baseline indicated improvement and a positive number change indicated worsening.
- Headache Impact Test (HIT-6) questionnaire — comprises six items that measure pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress. The total HIT-6 score range is from 36 to 78. The higher the score the more impact of the disease on the daily life of the respondent.
- Assessment of Chronic Migraine Impact (ACM-I) score and Assessment of Chronic Migraine Symptoms (ACM-S) — the ACM-I is a 24-item instrument that examines the effects of chronic migraine on a patient's life. Items include daily activities; feelings; energy level; household, leisure, and social activities; and work during the past seven days. The items are rated on a Likert scale of 0 (none of the time) to 5 (all of the time). The total ACM-I score was transformed so that higher scores indicated worse impact of chronic migraine. The ACM-S assesses the symptoms of chronic migraine and includes the domains of symptom severity and symptom experience.
- Acute headache pain medication use — defined as intake of medication(s) to treat headache pain.
- EuroQol-5D-3L (EQ-5D-3L) — is a generic HRQoL instrument that has been applied to a wide range of health conditions and treatments, including migraine. The EQ-5D-3L index score is generated by applying a multi-attribute utility function to the descriptive system. Scores less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively.
- Healthcare Resource Utilization (HRU) — refers to the patients' headache-related use of available health care resources and services.
- Serious AEs (SAEs), total AEs, withdrawal due to AEs, and notable harms.

The primary efficacy outcome for PREEMPT-1 was the frequency of headache episodes per 28-day period compared with baseline, while for PREEMPT-2 it was the frequency of headache days per 28-day period compared with baseline.

In the FORWARD trial, the primary efficacy end point was the proportion of patients with at least a 50% decrease from baseline in the frequency of headache days during a 28-day period, at the primary time point of week 32 (defined as the 28-day period ending with week 32). In Study 545, the primary efficacy end point was change from baseline in the ACM-I total score. In the COMPEL trial, the primary efficacy end point was the mean change from baseline in the number of headache days for the 28-day period ending at week 108 (following nine treatments). In the REPOSE, Negro et al. 2015 and Negro et al. 2016 no primary efficacy end point was defined.

Efficacy

Headache Impact Test-6

- The mean difference (MD) in change from baseline in total HIT-6 score favoured OnaA compared with placebo in both PREEMPT-1 (–2.3; 95% confidence interval [CI], –3.25 to –1.31) and PREEMPT-2 (–2.5; 95% CI, –3.54 to –1.55).
- Among patients with history of three or more prior prophylactics the mean (standard deviation [SD]) change from baseline in total HIT-6 score in the OnaA groups were [redacted] in PREEMPT-1 and PREEMPT-2, respectively. Differences between groups were statistically significant in both studies [redacted].
- In the FORWARD trial, at week 30, the mean (SD) changes from baseline for HIT-6 scores were −5.6 (7.2) for OnaA-treated patients and −1.3 (3.9) days for topiramate-treated patients, resulting in an estimated mean (95% CI) treatment difference of −4.248 (−5.766 to −2.731) in favour of OnaA ($P < 0.001$).
- In the COMPEL study, improvements from baseline on the mean HIT-6 total score were observed as early as week 12 (−4.4 [6.25]) and continued to week 60 (−6.8 [6.55]) and week 108 (−7.1 [7.24]; $P < 0.0001$ for all time points).
- In Negro et al. 2015 and Negro et al. 2016 the mean HIT-6 score decreased during the period of treatment from the first to the last injection (at baseline 69.4 ± 4.9, at 24 months 52 ± 5.6; $P < 0.001$ in Negro et al. 2015, and at baseline 67.9 ± 4.2, at 24 months 49 ± 6.7; $P < 0.001$ in Negro et al. 2016).

MSQ

- In both PREEMPT studies patients treated with OnaA had a greater decrease from baseline in mean scores for the three MSQ domains than patients treated with placebo. The change from baseline in MSQ subscales were reported as:
  - MSQ RFR scores: –16.8 versus –8.8 ($P < 0.001$) in PREEMPT-1 and –17.2 versus –8.4 ($P < 0.001$) in PREEMPT-2.
  - MSQ RFP scores: –12.6 versus –7.6 ($P = 0.005$) in PREEMPT-1 and –13.5 versus –5.4 ($P < 0.001$) in PREEMPT-2.
  - MSQ EF scores: –16.9 versus –10.0 ($P = 0.001$) in PREEMPT-1 and –19.0 versus –9.1 ($P < 0.001$) in PREEMPT-2.
- Similar findings for the MSQ were reported among patients with history of three or more prior prophylactics in the PREEMPT studies. The change from baseline in MSQ subscales were reported as:

  [redacted]

- In the COMPEL study, mean changes from baseline at week 108 were 18.4 ± 21.29 for the RFP domain, 26.1 ± 23.94 for the RFR domain, and 26.0 ± 26.23 for the EF domain.
- In the REPOSE study, improvements in all three MSQ domains were observed at all post-baseline treatment visits, based on patients with data available at baseline and the respective visit.

EQ-5D-3L

- In the REPOSE study, improvements in the EQ-5D-3L total score (index) were observed at all post-baseline treatment visits in the safety analysis set. The median total score was 0.69 (range: –0.59 to 1.0) at baseline (n = 596), the median total score was 0.76 (range: –0.32 to 1.0) at month six (n = 362) and 0.80 at all later visits, that is at month 12 (n = 227) and month 24 (n = 121), as well as at the last available follow-up visit (n = 424).

Improvement in headache/migraine days reductions in headache days per a 28-day period

- Patients treated with OnaA had a greater decrease from baseline in the frequency of headache days per a 28-day period at week 24 than those treated with placebo. The difference between OnaA and placebo in the least square (LS) mean change from baseline in frequency was:
  - PREEMPT-1: –1.4 ([redacted]), *P* = 0.006.
  - PREEMPT-2: –2.3 (95% CI, –3.25 to –1.31), *P* < 0.001.
- These differences appeared to be larger in the subgroup of patients with a history of three or more prior prophylactics in the PREEMPT studies. The change from baseline in headache days were reported as:

  [redacted]
- Patients treated with OnaA had a greater decrease from baseline in the frequency of migraine/probable migraine days per a 28-day period at week 24 than those treated with placebo. The difference between OnaA and placebo in the LS mean change from baseline in frequency was:

  [redacted]
- These differences appeared to be larger in the subgroup of patients with a history of three or more prior prophylactics in the PREEMPT studies. The change from baseline in migraine/probable migraine days were reported as:

  [redacted]
- There was no statistically significant difference between OnaA and placebo in change from baseline in the frequency of acute headache pain medication intake. The MD for OnaA versus placebo was [redacted] in PREEMPT-1 and [redacted] in PREEMPT-2.
- The difference between OnaA and placebo for the mean change from baseline in the frequency of headache episodes per a 28-day period at week 24 was [redacted] in PREEMPT-1 and [redacted] in PREEMPT-2.
- The difference between OnaA and placebo for the mean change from baseline in frequency migraine/probable migraine episodes per a 28-day period at week 24 was [redacted] in PREEMPT-1 and [redacted] in PREEMPT-2.
- The between-group difference in the mean change from baseline in total cumulative hours of headache at week 24 was approximately –30 hours in PREEMPT-1 and approximately –40 hours in PREEMPT-2 (*P* < 0.001), with less total cumulative hours of headache with OnaA.
- In the FORWARD trial, at the end of week 32, 40% of OnaA-treated patients demonstrated a ≥ 50% decrease from baseline in the mean number of headache days reported during weeks 29 to 32 versus 12.0% of topiramate-treated patients (odds ratio of 4.94; 95% CI, of 2.681 to 9.085; *P* < 0.001).
- In the COMPEL study, [redacted]
- In the FORWARD trial, during the interval from week 29 to week 32, the mean (SD) change from baseline in the number of headache days was −8.3 (8.9) days for OnaA-treated patients and −2.1 (5.6) days for topiramate-treated patients, resulting in an estimated mean treatment difference of –6.199 (95% CI, −7.936 to −4.462) headache days in favour of OnaA (*P* < 0.001).

- In the COMPEL trial, statistically significant reductions in the mean number of headache days from baseline were observed at week 108 (–10.7 [6.44] *P* < 0.0001).
- In the REPOSE trial, median number of headache days was below 10 days for the visits in predefined time windows: nine days at month six (n = 388), seven and a half days at month 12 (n = 250), six days at month 24 (n = 128), and eight days at last available follow-up visit (n = 455).
- In Negro et al. 2015 and Negro et al. 2016 the headache days per month decreased during the period of treatment from the first to the eighth session of therapy (at baseline 22.3 ± 4.1, at 24 months 7.3 ± 2.1; *P* < 0.001 in Negro et al. 2015, and at baseline 22.2 ± 4.9, at 24 months 4.1 ± 1.0; *P* < 0.001 in Negro et al. 2016).

Headache pain medication intake

[redacted]

- In the FORWARD trial, during weeks 29 to 32 of treatment, the mean (SD) change from baseline in the number of acute headache pain medication usage days was −5.5 (6.7) usage days for OnaA-treated patients versus −1.7 (5.2) usage days for patients treated with topiramate. The estimated mean treatment difference was −4.039 usage days in favour of OnaA over topiramate (95% CI, −5.387 to −2.691; *P* < 0.001).
- In Negro et al. 2015 and Negro et al. 2016 medication intake days decreased during the period of treatment from the first to the eighth session of therapy (at baseline 20.8 ± 4.5, at 24 months 5.3 ± 1.7 — *P* < 0.001 in Negro et al. 2015; and at baseline 21.0 ± 5.1, at 24 months 3.7 ± 1.3 — *P* < 0.001 in Negro et al. 2016).

Harms (Safety)

- The proportion of patients with at least one SAE was greater in the OnaA groups compared with the placebo groups:
  - PREEMPT-1: 5.3% with OnaA and 2.4% with placebo.
  - PREEMPT-2: 4.3% with OnaA and 2.2% with placebo.
- The proportion of patients with at least one AE was greater in the OnaA groups compared with the placebo groups:
  - PREEMPT-1: 59.7% with OnaA and 46.7% with placebo.
  - PREEMPT-2: 65.1% with OnaA and 56.4% with placebo.
- The proportion of patients who withdrew due to AEs were reported as follows:
  - PREEMPT-1: 4.1% with OnaA and 0.9% with placebo.
  - PREEMPT-2: 3.5% with OnaA and 1.4% with placebo.
- In the FORWARD study, the occurrence of AEs among topiramate-treated patients was higher than that in the OnaA treatment group (78.9% of patients in the topiramate group versus 47.7% for the OnaA group). Sinusitis, neck pain, eyelid ptosis, and migraine were the most frequently reported AEs for OnaA, whereas paresthesia, nausea, cognitive disorder and dizziness, and decreased appetite were among the most frequently reported AEs in the topiramate group.
- In Study 545, a total of nine (36.0%) patients in the OnaA group and [redacted] in the placebo group reported experiencing at least one AE.
- In the COMPEL study, AEs were reported in 60.9% (436 of 716) of patients. The most frequently reported (> 5%) were neck pain and sinusitis, [redacted]
- In the REPOSE study, adverse drug reactions (ADRs) were reported in 18.3% (116 of 633) of patients. The most frequently reported (> 5%) ADR was eyelid ptosis reported in 5.4% (34 of 633) of patients.
- In the FORWARD study, no single SAE was reported by more than one patient in either treatment group. SAEs were reported by 1.8% of patients in the OnaA treatment group, and in 4.2% of patients in the topiramate treatment group.

- In the COMPEL study, SAEs were reported in 10.5% of patients. The most frequently reported SAEs (that is in greater than or equal to three patients each) were migraine (0.8%); suicidal ideation (0.7%); and headache, malignant melanoma, and non-cardiac chest pain (0.4% each).
- In the REPOSE study, a total of nine SAEs were reported in eight patients (1.3%). [redacted]
- In the COMPEL study, discontinuations from the study due to AEs were reported in 4.5% of patients. The AEs leading to the most discontinuations were suicidal ideation (four patients) and eyelid ptosis, headache, and pregnancy (three patients each).
- There were no deaths in any of the included trials.
- The most common notable harms of interest experienced by patients receiving OnaA were neck pain, muscular weakness, and eyelid ptosis. The clinical expert indicated that the injection of OnaA may have caused neck pain because OnaA might have weakened the muscles in the neck, and then the neck has to work harder to hold up the head, causing pain (mainly muscular ache).

Indirect Treatment Comparisons

The Institute for Clinical and Economic Review conducted an ITC to examine calcitonin gene-related peptide inhibitors compared with placebo or commonly used preventive treatments in adults with chronic migraine. Although several efficacy and safety outcomes were evaluated, ITCs could be performed only for change from baseline in monthly migraine days, change from baseline in monthly headache days, and all-cause discontinuation. Using the Bayesian network meta-analysis, OnaA was not favoured over topiramate or calcitonin gene-related peptide inhibitors on these outcomes. These results, however, are limited by several potential sources of heterogeneity, which were not systematically evaluated and generalizability to the patient population of interest is limited.

Other Evidence

In the resubmission of OnaA to CADTH, the manufacturer provided evidence to support the clinical significance of the results from the PREEMPT studies addressing CDEC's concern regarding the uncertain clinical significance of OnaA effect in improving HRQoL and reducing the number of headache days and migraine/probable migraine days in patients with chronic migraine.

An article by Cole et al. describes estimates for MCIDs for between-group comparisons of the three domains of the MSQ (RFR, RFP, and EF). The treatment effect sizes associated with OnaA in the PREEMPT-1 and PREEMPT-2 trials for each of the MSQ domains, with the exception of EF in PREEMPT-1, all exceed the between-group MCIDs identified by Cole et al. However, the MCID's estimated by Cole et al. were based on patients with a maximum of 15 headache days per month (i.e., most patients in the datasets used by Cole et al. would be below the threshold for classification of chronic migraine). Hence, the MCID reported by Cole et al. might not be applicable for patients with chronic migraine, especially given that in most likelihood patients with chronic migraine would have worse HRQoL than patients with a maximum of 15 headache days per month, and hence an improvement in HRQoL that would be seen as clinically meaningful for patients with a maximum of 15 headache days per month might not be generalizable to patients with chronic migraine.

An article by Dodick et al., suggested that a one-day reduction in headache frequency was clinically meaningful. Dodick et al. referenced a study by Silberstein et al. Silberstein et al. stated that: "A 1-day increase in HA [headache] frequency was associated with a greater likelihood of headache pain interfering with mood (4.0%, $P < .001$), recreational activities (4.0%, $P = .004$), or life enjoyment (4.0%, $P = .001$)." It is unclear which instruments the domains of mood, recreational activities, or life enjoyment were taken from. As well, it is unclear if the domains were selected a priori or if a relationship between headache frequency and the other domains of HRQoL of the three instruments were also tested, found to be not statistically significant, and not reported. Without knowing the scale on which these domains were based, it is difficult to determine if a four per cent improvement was clinically meaningful. In addition, the time point and study sample size upon which these results are based are unclear.

Cost and Cost-Effectiveness

OnaA is available as a sterile, vacuum-dried, soluble concentrate powder that can be injected. Vial dosages are 50, 100, and 200 units, at a submitted list price of $178.50, $357.00, and $714.00, respectively. The recommended dose is 155 to 195 units of injection every 12 weeks, and the annual cost including wastage is $2,856 to $3,570.

The manufacturer submitted a cost-utility analysis that compared OnaA with BSC for the prophylaxis of headaches in adults with chronic migraine during a three-year time horizon from the perspective of a Canadian public health-care payer. The manufacturer also compared OnaA with topiramate in a pairwise scenario analysis to account for changes in clinical practice since the original submission. The Markov model attempted to address some of the previous limitations identified by CADTH. The manufacturer modelled 13 health states: six headache frequency health states based on headache days per month for each treatment status (i.e., on treatment, or discontinued treatment due to treatment failure); and, a death state. Efficacy and discontinuation data from the PREEMPT trials were pooled and used to inform transition probability for OnaA and BSC; placebo was used as a proxy for BSC. The manufacturer modelled response-based discontinuation on current clinical practice, where patients who do not experience at least a 50% reduction in headache frequency after the initial 24 weeks discontinue treatment. Patients discontinuing OnaA or BSC were assumed to be treated with BSC.

The manufacturer reported that OnaA compared with BSC resulted in an ICUR of $34,407 per QALY. OnaA was associated with 64% probability of being the optimal intervention compared with BSC at a willingness-to-pay threshold of $50,000 per QALY. As the focus of the manufacturer's resubmission was on new clinical data, the manufacturer presented a relevant scenario analysis that compared OnaA and topiramate based on the data from the FORWARD trial, and the placebo injection arm of the PREEMPT trials (for discontinuation). The manufacturer also conducted several scenario analyses in line with analyses in their original 2014 submission, including a subgroup analysis for patients with at least three prior oral prophylactic failures per the reimbursement request in the original submission, in which the ICUR for OnaA compared with BSC was $29,974 per QALY.

CADTH identified the following key limitations:

- The comparative clinical evidence for OnaA was associated with uncertainty. BSC was approximated using the placebo arm of the PREEMPT studies, and whether placebo reflects 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 that compared OnaA with topiramate, thus the cost-effectiveness estimate of OnaA compared with topiramate is uncertain.
- The manufacturer's model structure did not explicitly consider headache severity and may not appropriately capture clinically meaningful changes in migraine. The manufacturer also assumed patients who improved from chronic migraine to episodic migraine continued treatment, which may not be aligned with current clinical practice in Canada.
- Short-term data were extrapolated during the time horizon, which allow perpetual improvement and worsening of headache frequency. This is in contrast to clinical feedback that suggests the health state after initially responding to OnaA is likely to be maintained.

CADTH undertook the reanalyses using revised baseline characteristics, utility values, AE rates, long-term transition probabilities, and cost inputs. CADTH estimated that the ICUR of OnaA compared with BSC was $134,601 per QALY. A price reduction of more than 75% is required for OnaA to achieve an ICUR less than $50,000 per QALY compared with BSC. However, limitations with the comparative clinical effectiveness data and model structure could not be adequately addressed in the CADTH reanalyses. Based on these technical concerns and the focus of the manufacturer's resubmission on the full Health Canada population, reanalyses on the key population of interest considered in the recommendation were not conducted. The true cost-effectiveness of OnaA for the prophylaxis of chronic migraine is uncertain.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

April 10, 2019 Meeting (Initial)

Regrets

Two CDEC members did not attend.

Conflicts of Interest

None

September 18, 2019 Meeting (Reconsideration)

Regrets

One CDEC member did not attend.

Conflicts of Interest

None