CDEC FINAL RECOMMENDATION

ONABOTULINUMTOXINA
(Botox — Allergan Inc.)
Indication: Chronic Migraine

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that onabotulinumtoxinA (OA) not be listed for the management of chronic migraine.

Reason for the Recommendation:
1. Two randomized controlled trials (RCTs) (PREEMPT-1 and PREEMPT-2) demonstrated that OA was statistically superior to placebo for improving health-related quality of life and reducing the number of headache days and migraine/probable migraine days in patients with chronic migraine; however, the absolute difference between the OA and placebo groups was relatively small for this chronic condition (range of –1.4 to –2.3 headache days per 28-day period and –1.6 to –2.3 migraine/probable migraine per 28-day period).

2. There were significant limitations with the design of the PREEMPT-1 and PREEMPT-2 trials, such as the potential inclusion of patients with medication overuse headache, which precludes an accurate assessment of the clinical benefits of OA in the management of chronic migraine.

Background:
OA is a purified neurotoxin complex produced from the fermentation of Clostridium botulinum type A. It is indicated for the treatment of blepharospasm, strabismus, cervical dystonia, focal spasticity, equinus foot, bladder dysfunction, primary hyperhidrosis of the axillae, and chronic migraine. This Common Drug Review (CDR) submission is for the prophylaxis of headaches in adults with chronic migraine (≥ 15 days per month with headache lasting four hours a day or longer).

The recommended dosage of OA for the prophylaxis of chronic migraine is 155 units administered intramuscularly (0.1 mL injection [5 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.

Summary of CDEC Considerations

CDEC considered the following information prepared by CDR: a systematic review of RCTs focused on the use OA for the treatment of chronic migraine, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues that are important to individuals with chronic migraine.

Patient Input Information

The following is a summary of information that was provided by one patient group that responded to the CDR call for patient input:

- Individuals with chronic migraine report that their lives are "ruined" by headaches that are "almost always" there. Along with the physical symptoms, sufferers report difficulty with mentally challenging tasks, feelings of hopelessness and helplessness, guilt, stress, and depression. They report having to cancel work, social and family activities, and obligations when symptoms are severe. Some patients have given up making plans for the future.
- Currently there are no medications with a Health Canada-approved indication for the prophylaxis of chronic migraine. Patients report using medications that have not been approved for use in migraines. They may turn to controlled substances, massage therapy, acupuncture, physiotherapy, chiropractic treatments, aromatherapy, and products from health food stores. In general, patients are dissatisfied with current treatments and there is an unmet need for safe, effective, and universally available relief from the symptoms of chronic migraine.
- Patients hope that their lives would be improved with OA by decreasing the number of attacks, which they hope would then reduce the frequency of hospitalization and visits to emergency departments and either increase the number of days they can work or enable them to rejoin the workforce.

Clinical Trials

The CDR systematic review 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 per four-week period. Patients were randomized to receive 155 units of OA or placebo administered intramuscularly every 12 weeks. The duration of the double-blind treatment phase in both studies was 24 weeks.

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 28-day period
  - frequency of headache days per 28-day period
  - per cent reduction in migraine/probable migraine days per 28-day period
  - frequency of migraine/probable migraine days per 28-day period
  - frequency of moderate/severe headache days per 28-day period
  - total cumulative hours of headache occurring on headache days per 28-day period.
- Improvement in headache/migraine episodes — reported as the frequency of headache episodes per 28-day period and the frequency of migraine/probable migraine episodes per 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 health-related quality of life. The questionnaire comprises three domains: role function-restrictive (RFR), role function-preventive (RFP) and emotional function (EF). For each domain, scores range from 0 (high function) to 100 (low function).
- 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.
- Acute headache pain medication use — defined as intake of medication(s) to treat headache pain.
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

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.

Efficacy

- Patients treated with OA had a greater decrease from baseline in the frequency of headache days per 28-day period at week 24 than those treated with placebo. The difference between OA and placebo in the least square (LS) mean change from baseline in frequency was:
  - PREEMPT-1: –1.4 (99% CI, –2.72 to –0.09), $P = 0.006$.
  - PREEMPT-2: –2.3 (95% CI, –3.25 to –1.31), $P < 0.001$.
- Patients treated with OA had a greater decrease from baseline in the frequency of migraine/probable migraine days per 28-day period at week 24 than those treated with placebo. The difference between OA and placebo in the LS mean change from baseline in frequency was:
  - PREEMPT-1: –1.6 (99% CI, –2.91 to –0.27), $P = 0.002$.
  - PREEMPT-2: –2.3 (95% CI, –3.31 to –1.36), $P < 0.001$.
- There was no statistically significant difference between OA and placebo in change from baseline in the frequency of acute headache pain medication intake. The mean difference (MD) for OA versus placebo was –0.3 (95% CI, –2.99 to 2.29) in PREEMPT-1 and –1.60 (95% CI, –3.77 to 0.49) in PREEMPT-2.
- There was no statistically significant difference between OA and placebo in acute headache pain medication intake days in PREEMPT-1 (MD 0.0; 95% CI, –1.05 to 1.06); however, there was a statistically significant difference in PREEMPT-2 (MD –1.6; 95% CI, –2.50 to –0.71).
- The difference between OA and placebo for the mean change from baseline in the frequency of headache episodes per 28-day period at week 24 was –0.4 (99% CI, –1.36 to 0.63) in PREEMPT-1 and –1.0 (95% CI, –1.65 to –0.33) in PREEMPT-2.
- The difference between OA and placebo for the mean change from baseline in frequency migraine/probable migraine episodes per 28-day period at week 24 was –0.5 (99% CI, –1.45 to 0.50) in PREEMPT-1 and –1.0 (95% CI, –1.61 to –0.32) 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 OA.

- The MD in change from baseline in total HIT-6 score favoured OA compared with placebo in both PREEMPT-1 (–2.3; 95% CI, –3.25 to –1.31) and PREEMPT-2 (–2.5; 95% CI, –3.54 to –1.55).
- In both studies patients treated with OA 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: –17.2 versus –8.4 ($P < 0.001$) in PREEMPT-1 and –16.8 versus –8.8 ($P < 0.001$) in PREEMPT-2.
  - MSQ RFP scores: –13.5 versus –5.4 ($P < 0.001$) in PREEMPT-1 and –12.6 versus –7.6 ($P = 0.005$) in PREEMPT-2.
  - MSQ EF scores: –19.0 versus –9.1 ($P < 0.001$) in PREEMPT-1 and –16.9 versus –10.0 ($P = 0.001$) in PREEMPT-2.

Harms (Safety and Tolerability)

- The proportion of patients with at least one serious adverse event was greater in the OA groups compared with the placebo groups:
  - PREEMPT-1: 5.3% with OA and 2.4% with placebo.
  - PREEMPT-2: 4.3% with OA and 2.2% with placebo.
- The proportion of patients with at least one adverse event was greater in the OA groups compared with the placebo groups:
  - PREEMPT-1: 59.7% with OA and 46.7% with placebo.
  - PREEMPT-2: 65.1% with OA and 56.4% with placebo.
- The proportion of patients who withdrew due to adverse events were reported as follows:
  - PREEMPT-1: 4.1% with OA and 0.9% with placebo.
  - PREEMPT-2: 3.5% with OA and 1.4% with placebo.

Cost and Cost-Effectiveness

The manufacturer conducted a cost-utility analysis to assess OA compared with best supportive care (BSC) for the prophylaxis of headache in adults who have failed three or more oral prophylactic medications. This represents a subpopulation of the Health Canada-approved indication, which is not limited to use in patients who have failed prior therapy. Seven health states were included in the Markov model; six were based on the number of migraine days experienced per 28-day cycle and one was based on a discontinuation state. Clinical inputs were derived from pooling data from the PREEMPT studies (PREEMPT-1 and PREEMPT-2). Utility values for each health state were mapped from quality of life data from the PREEMPT studies to the EQ-5D (measure of health outcomes questionnaire). The time horizon for the analysis was set at three years with a cycle length of 12 weeks. A scenario analysis looking at the full Health Canada patient population was also presented by the manufacturer. The manufacturer reported that in patients who failed to respond to treatment with three or more oral prophylactic drugs, OA compared with BSC resulted in an incremental cost-utility ratio (ICUR) of $25,470 per quality adjusted life-year (QALY) gained, or $28,940 per QALY in the full Health Canada population.

The key limitations identified with the manufacturer's economic evaluation pertain to whether the model provides a good representation of the chronic nature of the condition and expected treatment, specifically:

- The economic model allowed patients to move to states representative of episodic migraine (< 15 headache days per month), a population for which OA is not indicated, which reflects a distinct clinical entity different from the chronic form. Patients improving to episodic states continued to receive treatment and incurred treatment costs and clinical benefits. The effects of including patients who no longer have chronic migraine could overestimate the benefits of OA.
- The inclusion of a 30% stopping rule to denote treatment failure is arbitrary. Treatment guidelines and CDR clinical guidance suggest that a 50% reduction or return to episodic migraine is the clinical goal of treatment.
- A three-year time horizon is short when capturing the implications of a chronic/long-term condition. OA is a preventive therapy, and continued treatment is needed for most patients to maintain treatment response; however, OA has not been studied beyond three years.
- The costs associated with physician visits, drug administration, and acquisition of OA were likely underestimated in the economic model.

As the model does not allow for reanalyses based on the first three limitations, significant uncertainty exists with respect to the likely ICUR. Considering more likely cost inputs alone increases the ICUR to $42,000 and $47,000 per QALY for the requested subpopulation and full Health Canada population respectively (CDR reanalyses).

At the submitted price of $3.57 per unit (dispensed as a 200 unit vial), the annual cost of OA ranges from $2,856 to $3,570 depending on the number of administrations per year (accounting for wastage of partially used vials).

Other Discussion Points:
CDEC noted the following:

- PREEMPT-1 and PREEMPT-2 did not specifically exclude patients suffering from medication overuse headache, which is a headache state that is distinct from chronic migraine.
- Patient group input indicated that many patients with chronic migraine cite a 50% reduction in headache days as a marker of efficacy, which was far below the effect size observed with OA in the PREEMPT-1 and PREEMPT-2 trials.

Research Gaps:
CDEC noted that there is insufficient evidence regarding the following:

- There are inadequate data regarding the long-term safety and efficacy of OA used for the prophylaxis of headaches in adults with chronic migraine.

CDEC Members:

Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

Regrets:
March 19, 2014: None

May 28, 2014: None

Conflicts of Interest:
March 19, 2014: None

May 28, 2014: None

About this Document:
CDEC provides formulary listing recommendations or advice to CDR participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

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