CDEC FINAL RECOMMENDATION

ONABOTULINUMTOXINA
(Botox — Allergan Inc.)
Indication: Overactive Bladder

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that onabotulinumtoxinA (Ona A) be listed for the treatment of overactive bladder (OAB) with symptoms of urinary incontinence, urgency, and frequency, in adult patients who have an inadequate response to or are intolerant of anticholinergic medication, if the following clinical criterion and conditions are met:

Clinical Criterion:

- Patients have had an adequate trial with at least two other pharmacologic treatments for OAB.

Conditions:

- Prescribing and administration is restricted to urologists.
- Funding should be limited to treatment with one dose to establish efficacy, and it should be discontinued in non-responders (i.e., those who fail to achieve a reduction of at least 50% in the frequency of urinary incontinence episodes with one dose).
- Limit to a maximum of three doses per year in responders, at a frequency of no more than once every 12 weeks.
- Reduction in price to improve the cost-effectiveness to an acceptable level.

Reason for the Recommendation:

1. Two phase 3 randomized controlled trials (RCTs) (study 095 [N = 557] and study 520 [N = 548]) conducted in adults with symptoms of idiopathic OAB who had not been adequately controlled with anticholinergic medications demonstrated that treatment with Ona A resulted in statistically significantly greater reductions from baseline in incontinence episodes, urge incontinence episodes, urgency episodes, micturition, and nocturia episodes compared with placebo.
2. Based on the Common Drug Review's (CDR) estimated incremental cost per quality-adjusted life-year (QALY) of $59,388 for Ona A, CDEC concluded that Ona A is not a cost-effective treatment option for OAB at the submitted price ($3.57 per unit).

Of Note:
CDEC noted that patients with OAB may benefit from behavioural training or lifestyle modification, and non-pharmacological approaches should be considered prior to the initiation of any drug therapy.

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Background:
Ona A 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, primary hyperhidrosis of the axillae, chronic migraine, neurogenic detrusor overactivity, and OAB. This CDR submission is for the treatment of OAB with symptoms of urinary incontinence, urgency, and frequency, in adult patients who have an inadequate response to or are intolerant of anticholinergic medication.

The recommended dosage for the treatment of OAB is 100 U, administered via injections into the detrusor muscle by cystoscopy across 20 sites of the bladder. Patients may be considered for re-treatment no sooner than three months from prior bladder injection when the clinical effect of the previous injection diminishes.

Summary of CDEC Considerations:
CDEC considered the following information prepared by the CDR: a systematic review of RCTs focused on the use of Ona A for the treatment of OAB, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues that are important to individuals living with OAB.

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:

- Those living with OAB reported that they have persistent fears about urine leakage (or losing complete control), such as when going from a seated to a standing position; that they have to identify the location of toilets along any routes they take, whether walking or riding; and that they frequently experience the associated feelings of embarrassment, reduced self-esteem, and a sense of loss of control over their lives. They may need to get up frequently at night to urinate, thus placing them at increased risk for reduced sleep quality as well as falls and fractures.
- Symptoms of urinary urgency and urge incontinence are the most important aspects of OAB to control.
- People living with OAB reported that anticholinergic medications were often discontinued due to poor tolerability (i.e., dry mouth, constipation, blurred vision, being unable to drive, cognitive impairment) or incomplete response to treatment. They also very much dislike having to wear pads, which, especially over the course of years, can be quite costly.
- Patients with OAB expect that a new drug would control their symptoms more effectively, have a lower risk of side effects compared with current treatments, improve their quality of life (including reducing their anxiety about urine leakage), improve their sleep quality, and be easier to take.

Clinical Trials
The systematic review included four multi-centre, double-blind RCTs comparing Ona A injection of 100 U with placebo. Study 095 (N = 557) and study 520 (N = 548) were phase 3 trials of up to 39 weeks' duration, but the placebo-controlled comparison was limited to 12 weeks, after which all patients could receive treatment with Ona A. Studies 077 (N = 313) and P030438 (N = 99) were phase 2 studies of 36 weeks' and six months' duration, respectively. Studies 095, 520, and 077 enrolled patients aged 18 years or older who had symptoms of idiopathic OAB with urge incontinence and who were not adequately managed with anticholinergic therapy. Study P030438 enrolled patients aged 18 years or older who had symptoms of idiopathic OAB with

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episodes of urgency with or without urge incontinence, and who were refractory, or had contraindications to, or discontinued anticholinergics because of adverse events. CDEC primarily focused its deliberations on the results of the two phase 3 trials (study 095 and study 520).

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following: change in the number of (i) incontinence episodes, (ii) urge incontinence episodes, (iii) urgency episodes, (iv) micturition events, and (v) nocturia episodes; quality of life; serious adverse events; total adverse events; and withdrawal due to adverse events. Symptoms and health-related quality of life (HRQoL) were measured using different scales in the trials, including the King's Health Questionnaire (KHQ), Incontinence Quality of Life Instrument (I-QOL), 12-Item Short-Form Health Survey (SF-12), and the European Quality of Life Scale Visual Analogue Scale (EQ-VAS). The co-primary efficacy outcome in studies 095 and 520 were mean change from baseline in the number of daily incontinence episodes and the proportion of patients with a positive treatment response at week 12.

Efficacy

- Patients treated with Ona A had a greater decrease from baseline in the number of daily incontinence episodes at week 12 compared with placebo. The difference between Ona A and placebo in least square (LS) mean change from baseline was:
  - Study 095: –1.65 (95% CI, –2.1 to –1.2), $P < 0.001$
  - Study 520: –1.91 (95% CI, –2.4 to –1.4), $P < 0.001$.
- In studies 095 and 520, patients treated with Ona A had a greater decrease from baseline in the number of daily urge incontinence episodes at week 12 compared with placebo. The difference between Ona A and placebo in LS mean change from baseline was:
  - Study 095: –1.66 (95% CI, –2.1 to –1.2), $P < 0.001$
  - Study 520: –1.97 (95% CI, –2.5 to –1.5), $P < 0.001$
  - In both studies, more than 60% of patients reported a ≥ 50% reduction in urge incontinence episodes, more than 48% had a ≥ 75% reduction, and more than 28% had a 100% reduction in urge incontinence episodes.
- Patients treated with Ona A had a greater decrease from baseline in the number of daily urgency episodes at week 12 compared with placebo. The difference between Ona A and placebo in LS mean change from baseline was:
  - Study 095: –1.51 (95% CI, –2.2 to –0.9), $P < 0.001$
  - Study 520: –2.44 (95% CI, –3.1 to –1.8), $P < 0.001$.
- Patients treated with Ona A had a greater decrease from baseline in the number of micturitions per 24 hours at week 12 compared with placebo. The difference between Ona A and placebo in LS mean change from baseline was:
  - Study 095: –1.04 (95% CI, –1.5 to –0.6), $P < 0.001$
  - Study 520: –1.72 (95% CI, –2.2 to –1.3), $P < 0.001$.
- Patients treated with Ona A had a greater decrease from baseline in the number of daily nocturia episodes at week 12 compared with placebo. The difference between Ona A and placebo in LS mean change from baseline was:
  - Study 095: –0.20 (95% CI, –0.38 to –0.02), $P = 0.029$
  - Study 520: –0.27 (95% CI, –0.47 to –0.08), $P = 0.007$.

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- Studies 095 and 520 reported statistically significant and clinically important improvements in disease-specific HRQoL measures (KHQ and I-QOL) for patients treated with Ona A versus placebo. Between-treatment differences in the SF-12, while statistically significant for the MCS and utility scores, were of uncertain clinical significance.

Harms (Safety and Tolerability)

- The proportion of patients with at least one serious adverse event was greater in the Ona A groups than in the placebo groups in studies 095 and 520:
  - Study 095: 3.2% with Ona A and 2.9% with placebo
  - Study 520: 4.7% with Ona A and 3.7% with placebo.
- The proportion of patients with at least one adverse event was greater in the Ona A groups than in the placebo groups:
  - Study 095: 61.5% with Ona A and 52.9% with placebo
  - Study 520: 51.8% with Ona A and 34.1% with placebo.
- The proportion of patients who withdrew due to adverse events was reported as follows:
  - Study 095: 1.4% with Ona A and 0.7% with placebo
  - Study 520: 0.7% with Ona A and 0.4% with placebo.
- The most frequent adverse events associated with Ona A were urinary tract infection, dysuria, urinary retention, bacteriuria, and increased residual urine volume.
- The proportion of patients receiving Ona A who required the use of clean intermittent catheterization for urinary retention was 6.1% and 6.9%, compared with 0% and 0.7% of patients receiving placebo, in studies 095 and 520, respectively.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis over a five-year time horizon comparing Ona A plus best supportive care (BSC), which included incontinence pads and treatment for adverse events such as skin and urinary tract infections, compared with BSC alone for the treatment of refractory urinary incontinence in adults with OAB. The analysis was based on a Markov model with five health states based on an average number of daily urinary incontinence episodes and a relative reduction in the average number of daily urinary incontinence episodes from baseline, and one absorbing state (death). Efficacy and transition probabilities were derived from patient level data from the pooled study data set of study 520 and study 095 and an extension trial (study 096). The duration of treatment effect was analyzed using the ongoing long-term extension study data (study 096); the median time to qualify for re-treatment was estimated at 34.10 weeks (approximately eight months). Utility values for each health state were obtained through mapping quality-of-life data captured in the clinical trials to the EQ-5D utility instrument. The manufacturer reported that the incremental cost per QALY for Ona A plus BSC was $34,029 compared with BSC alone.

CDR identified the following key limitations with the manufacturer's economic submission:

- The manufacturer assumed that Ona A would be discontinued after the first dose in non-responders (response was defined as ≥ 50% reduction in average daily number of urinary incontinence episodes). The clinical expert indicated that in practice, most clinicians would try a second dose prior to discontinuing therapy, which will increase the cost of Ona A.
- Use of different utility values between treatment arms within the same health state. This approach may lead to double-counting of benefits associated with Ona A.

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- The proportion of OAB patients receiving sacral nerve stimulation (SNS) and the time to initiation of SNS were informed by physician surveys that showed wide variability due to limited availability of urologists and medical centres that provide this procedure in Canada.
- The manufacturer assumed the efficacy of anticholinergics in patients in the BSC arm to be equivalent to placebo. Results from a published study showed that patients having failed previous anticholinergic therapy and receiving an additional anticholinergic had a greater reduction in daily urinary incontinence episodes than those receiving only placebo.

When accounting for these limitations, CDR found that the incremental cost-utility ratio for Ona A compared with BSC ranged from $56,932 to $60,451 per QALY gained, with a most likely estimate of $59,388 per QALY gained.

At the submitted price of $3.57 per unit, or $357 per 100 U vial, and depending on the frequency of re-treatment, the annual drug cost of Ona A varies from $357 (one injection per year) to $1,428 per year (one injection every three months). When administration costs are also considered, the total annual cost of Ona A exceeds that of second-line anticholinergics.

Other Discussion Points:
CDEC noted the following:

- CDEC expressed concern regarding the potential for urinary retention and the increased need for clean intermittent catheterization in patients treated with Ona A and noted that Ona A is contraindicated in patients who are not willing and able to have clean intermittent catheterization initiated.
- Studies 095 and 520 are limited by the short 12-week duration, the absence of an active comparator, and the use of only a single dose of Ona A.
- The clinical expert consulted by CDR indicated that the improvements in the daily frequency of incontinence, urge incontinence, and urgency were clinically relevant.

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

- There are inadequate data regarding the comparative long-term safety and efficacy of Ona A.

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

October 15, 2014 Meeting
Regrets:

None

Conflicts of Interest:

None

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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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