



## CDEC FINAL RECOMMENDATION

### ONABOTULINUMTOXINA

(Botox — Allergan Inc.)

**Indication: Neurogenic Detrusor Overactivity**

#### **Recommendation:**

The Canadian Drug Expert Committee (CDEC) recommends that onabotulinumtoxinA be listed 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) if the following conditions are met:

- patients fail to respond to behavioural modification and anticholinergics and/or are intolerant to anticholinergics
- subsequent treatments are provided at intervals no less than every 36 weeks.

The Committee further recommends that patients who fail to respond to initial treatment with onabotulinumtoxinA should not be retreated.

#### **Reasons for the Recommendation:**

1. In two phase 3 randomized controlled trials (RCTs) of patients with MS or SCI who have urinary incontinence due to detrusor overactivity and an inadequate response to anticholinergic agents, compared with placebo, onabotulinumtoxinA treatment resulted in statistically significant improvements in the frequency of urinary incontinence episodes, the proportion of patients achieving continence, and Incontinence Quality of Life (I-QOL) scores.
2. The manufacturer-submitted, cost-utility analysis reported an incremental cost per quality-adjusted life-year (QALY) of \$33,863 compared with best supportive care (BSC) for the pooled MS and SCI population, assuming a retreatment frequency of 66 weeks. Cost-effectiveness was considered unfavourable at retreatment frequencies of less than every 36 weeks.

#### **Of Note:**

The Committee noted that cost-effectiveness estimates are based on the assumption that patients who do not respond to onabotulinumtoxinA are not retreated. The definition for non-response employed in the economic analyses was < 50% reduction in the frequency of urinary incontinence episodes from baseline.

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### **Background:**

OnabotulinumtoxinA has a Health Canada indication for the treatment of urinary incontinence due to neurogenic detrusor overactivity resulting from neurogenic bladder associated with MS or subcervical SCI in adults who had an inadequate response to, or are intolerant of, anticholinergic medications.

OnabotulinumtoxinA is a neuromuscular paralytic agent. It is available in 50 unit (U), 100 U and 200 U vials. The Health Canada-recommended dose is 200 U administered into the detrusor muscle of the bladder across 30 sites.

### **Summary of CDEC Considerations:**

The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs of onabotulinumtoxinA, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

### **Clinical Trials**

The systematic review included three multicentre, double-blind RCTs comparing onabotulinumtoxinA injection of 200 U or 300 U with placebo in patients aged  $\geq 18$  years with urinary incontinence as a result of neurogenic detrusor overactivity associated with SCI or MS and inadequate response or intolerance to anticholinergic therapy.

- Studies 191622-515 (N = 416) and 191622-516 (N = 275), hereafter referred to as studies 515 and 516, were phase 3 trials of 52 weeks duration. After at least 12 weeks following initial treatment, all patients with  $< 50\%$  (study 515) or  $< 30\%$  (study 516) reduction from baseline in weekly episodes of incontinence were eligible to receive treatment with onabotulinumtoxinA, regardless of randomized treatment.
- Study 191622-511 (N = 59), hereafter referred to as study 511, was a phase 2 study of 26 weeks duration; no retreatment was allowed for the duration of the study.

In all trials, patients were required to continue pre-trial treatment with anticholinergic agents if they were so treated before study entry. In studies 515 and 516, the mean frequency of urinary incontinence episodes per week at baseline ranged from 28 to 32 and from 31 to 37, respectively. In study 511, the mean frequency of urinary incontinence episodes per day ranged from two to three.

For patients randomized to onabotulinumtoxinA or placebo, the frequency of study withdrawal, in studies 515, 516, and 511, was 19% versus 20%, 14% versus 15%, and 10% versus 0%, respectively. In studies 515 and 516, the median times to retreatment were 170 days and 180 days respectively, for patients randomized to onabotulinumtoxinA.

Limitations of the above trials include the possible overestimation of efficacy due to baseline frequency of urinary incontinence episodes that may be higher than generally observed in clinical practice. In addition, the lack of a specific definition for inadequate response to anticholinergic agents may introduce uncertainty as to which patients are appropriate candidates for onabotulinumtoxinA therapy in clinical practice.

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### **Outcomes**

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: change in frequency of urinary incontinence episodes, quality of life, adverse events, and withdrawal due to adverse events.

The primary efficacy outcome in all three studies was the change from baseline in the frequency of urinary incontinence episodes.

Quality of life was assessed using the I-QOL instrument, which produces a total summary score based on its three domains; avoidance and limiting behaviour, psychosocial impacts, and social embarrassment; higher scores are associated with greater quality of life.

### **Results**

Results are presented only for the Health Canada-recommended dose of 200 U and the Committee focused its discussion on the results of the two phase 3 trials, which are described below. Due to crossover from placebo to active treatment for a large percentage of patients, results are reported only up to week 12.

### **Efficacy or Effectiveness**

- Compared with placebo, onabotulinumtoxinA-treated patients reported statistically significantly greater reductions in the weekly frequency of urinary incontinence episodes in both studies 515 and 516 at week 12; mean difference (MD) (95% confidence interval [CI]), -11 (-14.9 to -7.2) and -8.9 (-14.5 to -3.2) respectively. Results were similar at week six.
- Compared with placebo, the percentage of patients achieving  $\geq 50\%$  reduction in the weekly frequency of urinary incontinence episodes at week 12 was statistically significantly greater for onabotulinumtoxinA in both trials; 76% and 79% versus 35%. Similarly, the percentage of patients achieving continence by week 12 was statistically significantly greater for onabotulinumtoxinA compared with placebo in both trials; 36% of patients in the onabotulinumtoxinA groups achieved 100% continence at week 12 compared with 7% and 9% in the placebo groups. Similar results were observed at weeks two and six in both trials.
- Compared with placebo, onabotulinumtoxinA significantly increased I-QOL total scores from baseline at weeks two, six, and 12 in both trials; however, the clinical significance of these results is uncertain.

### **Harms (Safety and Tolerability)**

- The incidence of serious adverse events was similar between onabotulinumtoxinA and placebo groups in all studies.
- Across all studies, the percentage of patients who withdrew due to adverse events was low in the onabotulinumtoxinA groups (range 1.1% to 3.9%).
- The most frequent adverse events across all included studies were urinary tract infection and urinary retention. The percentage of patients reporting urinary tract infection in onabotulinumtoxinA groups was 49% and 56% compared with 34% and 40% in placebo groups. The percentage of patients reporting urinary retention in onabotulinumtoxinA groups was 20% (in both trials) compared with 3% in both placebo groups.

- For patients not using clean intermittent catheterization (CIC) at baseline, there were noticeable increases in the proportion of patients using at least one CIC at weeks two, six, and 12 in the onabotulinumtoxinA groups compared with placebo in both trials.

### **Cost and Cost-Effectiveness**

The manufacturer conducted a cost-utility analysis to compare onabotulinumtoxinA plus BSC with BSC alone for the treatment of urinary incontinence due to neurogenic detrusor overactivity associated with MS or SCI over a five-year time horizon. BSC included anticholinergic agents, CIC, and incontinent pad use. The Markov model was comprised of six health states based on percent reduction in urinary incontinence episodes: 1) dry (100% reduction), 2) non-dry responders ( $\geq 50\%$  reduction), 3) non-responders ( $< 50\%$  reduction), 4) post-surgery dry (100% reduction), 5) post-surgery non-dry responders ( $\geq 50\%$  reduction), and 6) death. Patients who did not respond after the initial treatment were assumed to discontinue onabotulinumtoxinA. The manufacturer used pooled data from studies 515 and 516 to inform clinical efficacy inputs. Utilities were derived from the quality of life data elicited from the clinical trials (I-QOL index mapped to European Quality of Life-5 Dimension [EQ-5D]). The manufacturer reported that onabotulinumtoxinA plus BSC is associated with an incremental cost per QALY of \$33,863 compared with BSC alone for the pooled MS and SCI population.

CDR noted the following limitations with the manufacturer's analysis: the frequency of retreatment with onabotulinumtoxinA was assumed to be 66 weeks in the model, which is not supported by the product monograph or phase 3 clinical studies; and costs associated with use of incontinence pads is a key cost driver of the analysis, which may not be relevant for inclusion in an analysis conducted from the public-payer perspective. When addressing the above limitations, CDR found that the incremental cost per QALY estimates for onabotulinumtoxinA plus BSC compared with BSC alone were \$71,481 to \$78,676 for the pooled MS and SCI population, when considering a retreatment frequency of 36 to 42 weeks.

The average daily cost of onabotulinumtoxinA (200 U at a 36 to 42-week retreatment frequency, \$2.42 to \$2.79) is greater than anticholinergic agents (\$0.20 to \$1.85).

### **Patient Input Information:**

The following is a summary of information provided by one patient group that responded to the CDR Call for Patient Input. The patient group providing input was the Multiple Sclerosis Society of Canada; thus, the input provided is specific to MS patients.

- The third most common symptom mentioned by patients as having a major impact on their lives was bladder problems (after fatigue and difficulty walking). Specifically, the need to urinate frequently leads to a reluctance to leave the house and contributes to a reduced quality of life.
- Patients mentioned a number of anticholinergic medications that are used to manage bladder problems. However, only 10% of patients were satisfied with their current therapy. Dry mouth, constipation, and urinary infections were the most frequently reported side effects with the current therapies.
- Several patients who had experience with onabotulinumtoxinA noted that intradetrusor injections could be painful; however, they did not indicate that they refused further treatment because of it.

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- Patients would like to experience the following outcomes from a new therapy compared with their current therapy: reduced urgency of urination, reduced need to urinate during the day, to be able to sleep through the night, reduced leaking, and reduced need for incontinence pads.

### **Other Discussion Points:**

- The Committee considered that reduced costs associated with a potential decreased use of incontinence pads is an important outcome for patients.
- The Committee expressed concern regarding the potential for urinary retention and the increased need for CIC in patients treated with onabotulinumtoxinA. The Committee noted that onabotulinumtoxinA is contraindicated in patients who are not willing and/or not able to have CIC.
- The Committee noted that safety and efficacy data beyond two intradetrusor treatments of onabotulinumtoxinA are limited.
- The Committee noted that the mechanism of action of onabotulinumtoxinA is distinct from that of anticholinergic agents.

### **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. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

### **June 20, 2012 Meeting**

#### **Regrets:**

None

#### **Conflicts of Interest:**

None

#### **About this Document:**

CDEC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC made its recommendation. 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*.

The Final CDEC Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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