Common Drug Review
Pharmacoeconomic Review Report

July 2015

Drug	onabotulinumtoxinA for injection (Botox)
Indication	For the treatment of overactive bladder with symptoms of urinary incontinence, urgency, and frequency, in adult patients who have an inadequate response to or are intolerant of anticholinergic medication
Listing request	For the treatment of refractory urinary incontinence due to overactive bladder
Manufacturer	Allergan, Inc.

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ABBREVIATIONS

BSC	best supportive care
CDR	CADTH Common Drug Review
CIC	clean intermittent catheterization
EQ-5D	European Quality of Life Five Dimensions Questionnaire
ICUR	incremental cost-utility ratio
I-QOL	Incontinence Quality of Life Questionnaire
OAB	overactive bladder
Ona A	onabotulinumtoxinA
QALY	quality-adjusted life-year
SNS	sacral nerve stimulation
U	unit
UI	urinary incontinence
UIE	urinary-incontinence episode

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	OnabotulinumtoxinA (Botox)
Study Question	What is the cost-utility of Ona A 100 U injection plus BSC compared with BSC alone in the management of refractory UI due to OAB from the public payer perspective in Canada?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adults with UI due to OAB who are not adequately managed with anticholinergic medications.
Treatment	Ona A plus BSC
Outcome	QALY
Comparators	BSC (incontinence pad use and treatment for adverse events such as skin and urinary tract infections)
Perspective	Public payer
Time Horizon	5 years
Manufacturer's Results (Base Case)	$34,029 per QALY gained

Key Limitations and CDR Estimate(s)	• CDR noted a number of limitations with the manufacturer's model:
	  ○ The manufacturer assumed Ona A would be discontinued after the first dose in non-responders. The clinical expert indicated that, in practice, most clinicians would try a second dose prior to discontinuing therapy, which will increase Ona A treatment costs.
	  ○ Use of different utility values between treatment groups within the same health state, which results in double-counting of clinical benefits of Ona A, thus biasing the results in favour of Ona A.
	  ○ Overestimation of the proportion of patients receiving SNS, which overestimates total costs in the BSC group.
	  ○ Efficacy of anticholinergics in patients in the BSC group assumed to be equivalent to placebo, but some evidence suggests that in patients who receive another trial of anticholinergic despite previous failure, a greater reduction in UI episodes can be expected than if these patients receive no treatment.
	• When the above limitations are taken into account, CDR reanalyses estimate the ICUR for Ona A plus BSC to range from $56,932 to $60,451 per QALY, with the best estimate to be $59,388 per QALY based on the most likely scenario by CDR.

BSC = best supportive care; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; OAB = overactive bladder; Ona A = onabotulinumtoxinA; QALY = quality-adjusted life-year; SNS = sacral nerve stimulation; UI = urinary incontinence.

EXECUTIVE SUMMARY OF THE PHARMACOECONOMIC SUBMISSION

Background

OnabotulinumtoxinA (Botox) was submitted to the CADTH Common Drug Review (CDR) for review for the treatment of refractory urinary incontinence (UI) in adult patients with overactive bladder (OAB) who are not adequately managed with anticholinergic medications. OnabotulinumtoxinA (Ona A) is administered by injection at 100 units (U) intramuscularly into the detrusor muscle via cystoscopy. The submitted price is $3.57 per unit, or $357.00 per 100 U vial.

Depending on the frequency of re-treatment, the annual cost of Ona A varies from $357 (one injection per year) to $1,428 per year (one injection every three months).

Ona A was previously reviewed by CDR in 2012 for treatment of UI due to neurogenic detrusor overactivity resulting from neurogenic bladder associated with multiple sclerosis or sub-cervical spinal cord injury. The Canadian Drug Expert Committee recommended that Ona A be listed with conditions.[1]

Summary of Economic Analysis

The manufacturer submitted a cost-utility analysis of Ona A plus best supportive care (BSC), which included incontinence pads and treatment for adverse events such as skin and urinary tract infections (UTIs), compared with BSC alone for the treatment of refractory UI in adult patients with OAB. The analysis was based on a Markov model with five health states based on average number of daily UI episodes (UIE) and a relative reduction in the average number of daily UIE from baseline, and one absorbing state (death). Efficacy and transition probabilities were derived from patient-level data from the pooled study data set of two phase 3 trials (191622-520 and 191622-095) and an extension trial (191622-096). The duration of treatment effect was analyzed using the ongoing long-term extension study data (study 096); therefore, the median time to qualify for re-treatment was estimated at 34.1 weeks (approximately eight months). The proportion of patients receiving sacral nerve stimulation (SNS) was estimated based on physician surveys. Modelled adverse events included catheterization (duration and frequency of use) and UTI. Other adverse events such as bacteriuria, hematuria, and dysuria were either reported in low frequencies or are commonly accompanying symptoms of UTI and therefore were not modelled separately. The manufacturer captured treatment costs associated with Ona A and BSC, as well as costs of medical resource utilization. Utility values for each health state were obtained by mapping the quality of life data captured in the clinical trials to the EQ-5D utility instrument. The time horizon for the analysis was set at five years, with a cycle length of 12 weeks (i.e., three months).

Results of Manufacturer's Analysis

The manufacturer reports that the incremental cost per QALY for Ona A plus BSC was $34,029 compared with BSC alone.

Interpretations and Key Limitations

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

- **Stopping rule for non-responders to Ona A:** The manufacturer assumed that Ona A would be discontinued after the first dose in non-responders. The clinical expert indicated that, in practice, most clinicians would try a second dose prior to discontinuing therapy, which will increase Ona A costs.
- **Use of different utility values between treatment groups within the same health state:** The manufacturer's rationale for this approach was to capture additional benefits in terms of micturition and nocturia associated with Ona A.[2] However, this approach introduces the impact of treatment benefits of Ona A that were not the outcomes of interest in the submitted economic evaluation, which may lead to double-counting of the benefits associated with Ona A. CDR sensitivity analyses using uniform utility values for both treatment groups within the same health state produced an ICUR range of $43,914 to $91,536 per QALY.
- **Inappropriate estimation of the frequency and time to receive SNS:** The proportion of OAB patients receiving SNS (23%) and the time to initiation of SNS (two months) were informed by physician surveys that showed wide variability due to limited availability of urologists and medical centres that provide SNS in Canada. The clinical expert involved in this review indicated that only a small number of centres and clinicians perform SNS in Canada. The manufacturer's estimate may not be reflective of actual clinical practice; therefore, CDR sensitivity analyses were performed using estimates based on clinical expert opinion. The CDR reanalyses produced an ICUR range of $56,728 to $60,144 per QALY.
- **Efficacy of anticholinergics in patients in the BSC group assumed to be equivalent to placebo:** The manufacturer acknowledged that, in the absence of Ona A as a treatment option for UI refractory to anticholinergic medications, use of anticholinergics will likely continue in real life, but assumed the efficacy of anticholinergics would not be superior to placebo. Results from a published study from Khullar et al. showed that patients, having failed previous anticholinergic therapy and receiving tolterodine (an anticholinergic), had a greater reduction in daily UIE versus those receiving only placebo.[3] In a CDR sensitivity analysis in which BSC patients continued anticholinergic use but experienced a response rate 10% greater than that of placebo, the ICUR increased to $57,986.

Results of CADTH Common Drug Review Analysis

CDR reanalyses considering the stopping rule for Ona A, health state utility values, proportion of SNS patients, time to SNS treatment, and anticholinergic use in the BSC group, produced ICURs ranging from $56,932 to $60,451 per QALY gained. In a CDR analysis on the most likely scenario, the ICUR for Ona A plus BSC increased to $59,388 per QALY gained.

Conclusions

A key limitation was the manufacturer's modelling of health state utilities. Other limitations include the stopping rule for Ona A, proportion of patients receiving SNS, time to initiation of SNS, and efficacy of anticholinergics in the BSC group compared with real-life clinical practice. When accounting for these limitations, CDR found that the ICUR of Ona A plus BSC compared with BSC alone ranged from $56,932 to $60,451 per QALY gained, with a most likely ICUR estimate of $59,388 per QALY gained. The place in therapy and cost-effectiveness of Ona A compared with mirabegron is unclear at this time.

REVIEW OF THE PHARMACOECONOMIC SUBMISSION

1. INTRODUCTION

1.1 Study Question

"What is the cost-utility of BOTOX 100 U injection and best supportive care (BSC) compared to BSC alone in the management of refractory UI due to OAB from the public payer perspective in Canada?"

(Manufacturer's Pharmacoeconomic Submission, page 3.[2])

1.2 Treatment

OnabotulinumtoxinA (Ona A; Botox) is administered at a recommended dose of 100 U injected into the detrusor muscle, in combination with BSC, which consists of incontinence pads and treatment for adverse events such as skin and urinary tract infections (UTIs).

1.3 Comparators

The economic evaluation submitted by the manufacturer compared Ona A in combination with BSC (incontinence pads and treatment for adverse events such as skin and UTIs) with BSC alone.

1.4 Type of Economic Evaluation

The manufacturer submitted a cost-utility analysis (CUA) as per CADTH's *Guidelines for Economic Evaluations of Health Technologies: CADTH*. The analysis takes a ministry of health perspective. The manufacturer also submitted a CUA from the societal perspective.

1.5 Population

The target population for this economic evaluation comprises adult patients with overactive bladder (OAB) with urinary incontinence (UI) that is not adequately managed with anticholinergic medications. This is in line with the Health Canada indication. The baseline patient and disease characteristics for the target population were derived from two phase 3 studies (191622-095 and 191622-520)[4,5] and an Ona A extension trial (191622-096).[6] Mean age at baseline was 60.4 years.[2]

2. METHODS

A CUA was conducted using a Markov transition model to assess the cost-effectiveness of Ona A plus BSC compared with BSC in the treatment of refractory UI in adult patients with OAB. The three-month Markov cycle duration was consistent with the time points at which outcomes were measured in the phase 3 trials (095 and 520)[4,5] (i.e., measurements repeated at 12-week intervals). This duration (three months) was also the minimum time interval required between two Ona A administrations in the phase 3 trials (095 and 520).[4,5]

2.1 Model Structure

The manufacturer submitted a Markov transition model that simulates the course of adult OAB patients with refractory UI not adequately managed on anticholinergic medications receiving Ona A. The health state transition model comprises five health states based on the average number of daily urinary-incontinence episodes (UIE) (collected through three-day diaries in the clinical trials) and relative reduction in the average number of daily UIE from baseline, and death:

- Dry (i.e., 100% reduction in UIE from baseline and zero UI episodes)
- 50% to 99% reduction in UIE and > 1UIE
- 50% to 99% reduction in UIE and ≤ 1 UIE
- < 50% reduction in UIE and > 1 UIE
- < 50% reduction in UIE and > 1 UIE
- Death (absorbing state).

After each cycle, patients could stay in the same health state or move to any of the five other health states (death was an absorbing state).

2.2 Clinical Inputs

2.2.1 Efficacy

Transition probabilities were informed from the patient-level data from a pooled study data set of phase 3 clinical trials (191622-095 and 191622-520) and an extension trial (191622-096).[4-6] Patient-level data were analyzed until study day 365; i.e., the end of model cycle 4. The pooled study data set for the Ona A and placebo groups was analyzed only in patients who started the study in Ona A and placebo groups and remained there until the last time point of the analyses (i.e., all patients who crossed over from a placebo to Ona A group were not included in any of the Ona A analyses).

a) Cycle 1

Ona A and BSC patients at the start of the model are distributed across health states based on the proportion of patients in the Ona A and placebo groups during the placebo-controlled period from the two phase 3 trials (191622-520 and 191622-095).[4,5] The proportion of patients at the end of model cycle 1 served as the basis for transition probabilities applied in subsequent model cycles in the Ona A group (Table 2).

TABLE 2: PROPORTION OF PATIENTS ACROSS MODEL HEALTH STATES AT MODEL ENTRY AND AT THE END OF MODEL CYCLE 1

Health State	Ona A 100 U		BSC	
	Baseline	End of cycle 1	Baseline	End of cycle 1
Dry	0%	28.9%	0%	8.1%
50% to 99% reduction and ≤ 1 UIE	0%	18.9%	0%	11.3%
50% to 99% reduction and > 1 UIE	0%	14.3	0%	12.6%
< 50% reduction and ≤ 1 UIE	3.8%	2.9%	3.5%	2.8%
< 50% reduction and > 1 UIE	96.2%	35.0%	96.5%	65.2%

BSC = best supportive care; Ona A = onabotulinumtoxinA; UIE = urinary-incontinence episode.
Source: Manufacturer's Pharmacoeconomic Evaluation Report, Table 8, page 43.[2]

b) Cycles 2 to 4

Ona A group: Transition probabilities per health state were derived as an average of transition probabilities at model cycles 2, 3, and 4 in patients who had remained in the Ona A group and continued to receive therapy (Table 3). It was assumed that patients who discontinued Ona A treatment would remain on BSC in the Ona A group of the model and be distributed across health states based on the proportion of patients in the BSC group at model cycle 1. It was assumed that patients would remain in the same health state on BSC therapy for the rest of the time horizon, unless they were offered treatment with sacral nerve stimulation (SNS); 23% of patients on BSC therapy with < 50% reduction in average UI episodes from baseline would be offered the opportunity to initiate therapy with SNS.

BSC group: Efficacy in BSC group of the model was based on the data from the placebo group at model cycle 1 from the pooled study data set (studies 520, 095, and 096). It was assumed that BSC patients who remained on BSC therapy would remain in their model cycle 1 health states, including an associated number of average daily UIE and health-related quality of life through the whole time horizon of the analysis. Patients in the BSC group do not transition to subsequent model cycles. For modelling of SNS treatment in the BSC group, an identical approach was assumed as in the Ona A group: 23% of patients with < 50% reduction in average UI episodes from baseline would be offered to SNS.

c) Cycle 5 and Onward

In the Ona A group, it was assumed that patients would move across health states in model cycles 5 and onward (get better or get worse) in an identical manner to how they moved between health states in model cycles 2 to 4. For the BSC group, it was assumed that patients would remain in their model cycle 1 health states, including health-related quality of life and the associated number of average daily UIE through the whole time horizon of the analysis.

TABLE 3: PATIENT TRANSITION PROBABILITIES FROM CYCLE 2 AND ONWARD (ONA A)

		From Health State				
		Dry	**50% to 99% Reduction and ≤ 1 UIE**	**50% to 99% Reduction and > 1 UIE**	**< 50% Reduction and ≤ 1 UIE**	**< 50% Reduction and > 1 UIE**
To Health State	**Dry**	57.1%	29.4%	14.4%	14.3%	19.9%
	50% to 99% reduction and ≤ 1 UIE	24.4%	32.9%	19.0%	14.3%	14.3%
	50% to 99% reduction and > 1 UIE	6.1%	20.8%	44.1%	0.0%	19.3%
	< 50% reduction and ≤ 1 UIE	1.1%	0.0%	0.0%	14.3%	0.6%
	< 50% reduction and > 1 UIE	11.4%	16.9%	22.6%	57.1%	46.0%

Ona A = onabotulinumtoxinA; UIE = urinary-incontinence episode.
Source: Manufacturer's Pharmacoeconomic Evaluation Report, Table 9, page 44.[2]

The pooled study data set (studies 052, 095, and 096) was used to calculate the average number of daily UIE for all patients in each health state, to account for resource utilization (incontinence pad) associated with UIE. Study data at the end of each model cycle were analyzed to capture all available study measurements within specified time intervals (e.g., from day 0 to 91 for model cycle 1). Hence, the number of daily UIE at model cycle 1 represents an average value of all study measurements within that time period. For example, the average value of UIE measurements recorded for days 14, 42, and 84 represents the number of UIE for model cycle 1. The study data were analyzed for average number of UIE per day per patient.

2.2.2 Ona A Re-treatment

The product monograph for Ona A reported the duration of clinical effect at 166 days (approximately 24 weeks or six months).[7] However, the manufacturer indicated that Canadian urologists with experience using Ona A for this indication have noted a longer time to re-treatment in their clinical practice and that the duration of effect reported in the product monograph may be an artifact of the trial design, and that the trial protocol may have predisposed patients who had received their first Ona A treatment within the pivotal trials to request and receive re-treatment sooner than they would have otherwise. Therefore, 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 34.1 weeks (approximately eight months). As such, an eight-month re-treatment interval was used in the model.

a) Harms

Modelled adverse events (AEs) included catheterization (duration and frequency of use) and UTI. Other AEs such as bacteriuria, hematuria, and dysuria were either reported in low frequencies (see CDR Clinical Report), or are commonly accompanying symptoms of UTI and therefore were not modelled separately. The manufacturer stated that clinical trial data indicate that Ona A patients who had one or more of the most common adverse events (UTI, urinary retention, and initiation of clear intermittent catheterization [CIC]) were just as likely to request and qualify for re-treatment as patients who had

none of the three adverse events. The manufacturer also pointed out that, based on data from the phase 3 trials suggesting comparable quality of life scores in Ona A patients who had an adverse event compared with those without an adverse event, no disutility was applied to adverse events.[2]

2.3 Costs

The manufacturer included costs and resource use associated with intervention screening, Ona A administration, and management of adverse events. The costs were derived from a variety of sources: the Ontario Schedule of Benefits for Physician Services, the Ontario Case Costing Initiative, the Ontario Drug Benefit Program, and a survey of physicians. The submitted model also offers the possibility of estimating cost-effectiveness from the societal perspective by including indirect costs due to productivity lost.

Drug Costs

The cost of Ona A was provided by the manufacturer at $357 per each 100 U dose. There was no treatment cost in the BSC comparator group, as costs associated with incontinence pads and CIC are not widely reimbursed by public drug plans in Canada.

Adverse Events

Costs associated with adverse events were accounted for by the manufacturer; the medication cost of treating UTIs and the medical care of training patients on CIC use were included in the base-case analysis.

2.4 Utilities

Utilities were derived from the quality of life data elicited from the clinical trials (191622-520, 191622-095, and 191622-096). The clinical trials used the Incontinence Quality of Life (I-QOL) questionnaire. The I-QOL is a validated, disease-specific instrument that has three disease-specific domains (avoiding and limiting behaviour, psychosocial impacts, and social embarrassment) that capture the health-related quality of life impact of UI on the patient. The utilities for the model health states were derived by mapping the results from the I-QOL to the EQ-5D. The mapping algorithm and methodology are as presented in Kay et al. 2013.[8] The derived mapped utility values are presented in Table 4.

The utility in each health state in model cycle 1 is an average of Ona A and BSC utility estimates captured from baseline until the end of model cycle 1. These utility estimates were derived from I-QOL measurements captured at baseline and at week 12 post-treatment from patients randomized to the Ona A group and BSC in the clinical trials. For the Ona A group, the manufacturer indicated that utility in each health state in model cycle 2 and onward is an average of all Ona A utility estimates from the beginning of model cycle 2 to the end of model cycle 4 in Ona A patients available at the end of model cycle 4 in the clinical trials. For the BSC group, placebo data are available only up to model cycle 1; therefore, utilities in model cycle 2 and onward are assumed to be the same as in the previous model cycle.

TABLE 4: HEALTH STATE UTILITY SCORES PER TREATMENT GROUP AND HEALTH STATE — EQ-5D MAPPED FROM I-QOL

Health State	Model Cycle 1			
	Ona A		BSC	
	Mean utility per health state	SD	Mean utility per health state	SD
Dry	0.920	0.052	0.895	0.058
50 to 99% reduction and ≤ 1 UIE	0.871	0.076	0.856	0.067
50 to 99% reduction and > 1 UIE	0.831	0.074	0.816	0.083
< 50% reduction and ≤ 1 UIE	0.828	0.059	0.852	0.046
< 50% reduction and > 1 UIE	0.789	0.075	0.784	0.069
	Model Cycle 2+			
	Ona A		BSC	
	Mean utility per health state	SD	Assumed to be the same as for model cycle 1	
Dry	0.895	0.059		
50 to 99% reduction and ≤ 1 UIE	0.870	0.068		
50 to 99% reduction and > 1 UIE	0.845	0.066		
< 50% reduction and ≤ 1 UIE	0.846	0.056		
< 50% reduction and > 1 UIE	0.826	0.078		

BSC = best supportive care; EQ-5D = European Quality of Life Five-Dimensions Questionnaire; I-QOL = Incontinence Quality of Life; Ona A = onabotulinumtoxinA; SD = standard deviation.
Source: Adapted from Manufacturer's Pharmacoeconomic Report, Table 17, page 55.[2]

The manufacturer provided justification for the use of different utilities across treatment groups; an analysis of the clinical trial data indicated that Ona A patients in any health state had better I-QOL scores and greater self-reported treatment benefit compared with placebo patients in the same health state. This may be attributed to Ona A treatment conferring additional benefits to patients, while the model health state is defined only in the frequency of UI.

The manufacturer also pointed out that patients in the Ona A group experienced significantly greater improvement in a number of symptoms, including the frequency of micturition and nocturia episodes compared with the placebo group (see CDR Clinical Report). Therefore, to capture additional benefits in terms of micturition and nocturia associated with Ona A therapy, the manufacturer calculated utility values separately for each health state and per treatment group.

2.5 Time Horizon

The model time horizon for the base-case analysis was set at five years using a cycle duration of three months. The submitted model allows comparison of cost and health outcomes over any time horizon from six months to the patient's lifetime. The model also allows assessing costs and benefits of two treatment alternatives in a lifetime analysis.

2.6 Discounting

A discount rate of 5% was applied to both health and economic outcomes. A sensitivity analysis of the base-case scenario was conducted with no discounting (discount rate of 0%) and a discount rate of 3%, as recommended by the CADTH guidelines.

2.7 Validation

No formal validation was conducted by the manufacturer.

3. RESULTS

3.1 Manufacturer's Base Case

The manufacturer's base-case analysis in the submission was an analysis of Ona A versus BSC in OAB patients under a reference scenario; patients who do not achieve adequate response (response to therapy defined as ≥ 50% reduction in UI episodes from baseline) after their first injection discontinue therapy and receive BSC. Under the reference scenario, patients receiving Ona A experienced 565 fewer UI episodes per year compared with a BSC patient. Clinical improvement in UI episodes translated to 3.778 QALYs gained with Ona A versus 3.642 QALYs gained with BSC over five years. Thus, there is an incremental gain of 0.136 QALYs achieved with Ona A therapy. This resulted in an incremental cost per QALY of $34,029 (Table 5). Other key results of the base-case analysis are summarized in Table 6.

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

	Costs ($)	Incremental Costs ($)	QALYs	Incremental QALYs	ICUR ($/QALY)
Ona A	$6,484	$4,633	3.778	0.136	$34,029
BSC	$1,851	NA	3.642	NA	reference

BSC = best supportive care; ICUR = incremental cost-utility ratio; NA = not applicable; Ona A = onabotulinumtoxinA; QALY = quality-adjusted life-year.
Source: Manufacturer's Pharmacoeconomic Report, Table 25, page 72.[2]

TABLE 6: KEY RESULTS FROM BASE-CASE ANALYSIS

	Ona A	BSC	Difference
Number of events per patient per year			
Number of UIE	907	1,471	−565
Number of UTI	1	0.3	0.6
Number of follow-up physician visits	4.08	4.54	−0.47
Incontinence pad use	907	1,471	−565
CIC use	8	0.6	7.4
Costs (5 years, discounted)			
Total direct costs	$6,484	$1,851	$4,633
Total intervention costs	$5,823	$0	$5,823
Intervention drug costs	$1,929	$0	$1,929
Intervention administration costs	$3,809	$0	$3,809
Urodynamic tests	$85		
BSC costs			
Downstream SNS costs	$159	$1,341	−$1,165
Follow-up physician visit costs	$480	$520	−$40
Adverse event costs			
UTI costs	$21	$7	$14

BSC = best supportive care; CIC = clean intermittent catheterization; ICUR = incremental cost-utility ratio; Ona A = onabotulinumtoxinA; QALY = quality-adjusted life-year; SNS = sacral nerve stimulation; UIE = urinary-incontinence episode; UTI = urinary tract infection.
Source: Manufacturer's Pharmacoeconomic Report, Table 25, page 72.[2]

3.1.1 Scenario Analysis

The manufacturer also undertook a scenario analysis in which Ona A patients are offered a second injection prior to deciding on treatment discontinuation. In this analysis, Ona A resulted in an incremental cost per QALY of $38,387 versus BSC (Table 7).

TABLE 7: SUMMARY OF RESULTS OF THE MANUFACTURER'S SCENARIO ANALYSIS

	Costs ($)	Incremental costs ($)	QALYs	Incremental QALYs	ICUR ($/QALY)
Ona A	$7,286	$5,434	3.784	0.142	$38,387
BSC	$1,851	NA	3.642	NA	reference

BSC = best supportive care; ICUR = incremental cost-utility ratio; NA = not applicable; Ona A = onabotulinumtoxinA; QALY = quality-adjusted life-year.

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 a sensible range of values, 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 all scenarios falling under the $50,000 per QALY willingness-to-pay threshold. Using utilities directly elicited from individuals results in the lowest estimated ICUR ($11,104); assuming a re-treatment interval of 5.45 months results in the highest estimated ICUR ($49,071). The manufacturer identified the source of utility estimates,

average time to Ona A re-treatment and scenario of Ona A re-treatment as the sources of highest uncertainty.

Probabilistic Sensitivity Analyses
A probabilistic sensitivity analysis was performed using 1,000 iterations. The manufacturer reported that more than 60% of iterations fell below a willingness-to-pay threshold of $50,000 per QALY.

3.3 CADTH Common Drug Review Analyses

3.3.1 Health States Utility Values

The manufacturer's rationale for differential utility per health state across treatment groups was to capture additional benefits in terms of micturition and nocturia associated with Ona A therapy, based on trial data indicating Ona A patients in any health state had better I-QOL scores and greater self-reported treatment benefit compared with placebo patients in the same health state.[2] This approach introduces the impact of treatment benefits of Ona A that were not the outcomes of interest in the submitted economic evaluation (health states were defined based on relative reduction and absolute number of daily UIEs), and may result in double-counting of Ona A benefits. CDR sensitivity analyses using uniform utility values across the model's health states produced ICURs ranging from $43,914 per QALY (using utility values from Ona A at the end of cycle 1) to $91,536 per QALY (using utility values from Ona A at cycle 2 of the base case; i.e., non-responders who do not receive additional doses of Ona A).

3.3.2 Proportion of Patients Receiving Sacral Nerve Stimulation and Time to Sacral Nerve Stimulation Treatment

The manufacturer acknowledged a wide variability in the results of the physician surveys conducted; although most urologists in Canada do not perform SNS, those who do reported high estimates.[2] The clinical expert on this review confirmed that issues with the availability and accessibility to urologists who specialize in performing SNS leads to increased waiting time for getting the treatment and, consequently, reduced the proportion of OAB patients receiving SNS. CDR sensitivity analyses on the proportion of patients receiving SNS and the time to SNS treatment were performed using estimates based on clinical expert opinion. The CDR reanalyses produced an ICUR range of $56,728 to $60,144 per QALY (Table 8).

3.3.3 Use of Anticholinergics in the Best Supportive Care Group

The manufacturer acknowledged that approximately 40% of patients will likely continue anticholinergics in real life (which was also consistent with the clinical expert's opinion), but considered that the efficacy of anticholinergics would not be superior to placebo, and did not include costs or efficacy related to use of anticholinergics.[2] Results of the SCORPIO study (which aimed to evaluate the efficacy and safety of the beta-3 agonist mirabegron in OAB patients) showed that patients having failed previous anticholinergic therapy and receiving tolterodine had a greater reduction in daily UIE versus those receiving only placebo.[3] In a sensitivity analysis in which CDR assumed 40% of patients on anticholinergics (and using the average monthly cost as per manufacturer's report, $46.80), but varying the response rate in the BSC group at the end of cycle 1 by 10% as per the SCORPIO study, the ICUR increased to $57,986.

TABLE 8: RESULTS OF CDR REANALYSES ON SNS AND ANTICHOLINERGICS (ICUR, $/QALY, ONA A VERSUS BSC)

% SNS	Efficacy of Anticholinergics = Placebo, No Cost[a]				Average monthly cost for anticholinergics: $46.80 Efficacy of Anticholinergics = Placebo[a]				Average monthly cost for anticholinergics: $46.80 Efficacy of Anticholinergics = 10% > Placebo[a]			
	Time to SNS Procedure (Mo)				Time to SNS Procedure (Mo)				Time to SNS Procedure (Mo)			
	2 mo	6 mo	8 mo	12 mo	2 mo	6 mo	8 mo	12 mo	2 mo	6 mo	8 mo	12 mo
5%	$60,144	$60,047	$59,950	$59,964	$51,541	$51,458	$51,372	$51,395	$60,451	$60,343	$60,235	$60,246
10%	$59,513	$59,317	$59,120	$59,151	$50,728	$50,562	$50,387	$50,438	$59,828	$59,608	**$59,388**[b]	$59,414
15%	$58,839	$58,541	$58,243	$58,294	$49,860	$49,609	$49,346	$49,431	$59,160	$58,825	$58,490	$58,535
20%	$58,119	$57,716	$57,313	$57,391	$48,932	$48,596	$48,243	$48,367	$58,443	$57,988	$57,535	$57,604
23%	$57,662	$57,195	$56,728	$56,824	$48,343	$47,957	$47,550	$47,701	$57,986	$57,459	$56,932	$57,020

BSC = best supportive care; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; mo = months; Ona A = onabotulinumtoxinA; QALY = quality-adjusted life-year; SNS = sacral nerve stimulation.

[a] All the CDR reanalyses described in Table 8 are based on the scenario in which patients are offered a second injection prior to deciding on treatment discontinuation

[b] CDR most likely scenario.

a) Most Likely Scenario

A CDR reanalysis was conducted wherein the health state utility values for BSC were applied throughout the model for both treatment groups (Table 4). This revised model will allow Ona A patients who are not responding to receive re-treatment for a second dose before determining treatment efficacy. This is based on clinical expert opinion indicating that variability in response could be due to Ona A not being injected properly or not being absorbed; therefore, if no improvement is detected after three months, a second administration of Ona A would be needed. The scenario will also assume that 10% of patients will receive SNS after a median duration of eight months; this reflects real-life practice and the limited availability of and accessibility to SNS in Canada.[9,10] Finally, the scenario will assume that 40% of BSC patients will continue using anticholinergics and will show a response rate of 10%. The ICUR for Ona A under the most likely scenario increased from $34,029 to $59,388 per QALY gained.

3.3.4 Pricing Analysis

Given the level of uncertainty in the results, a price analysis was undertaken to determine the price reduction required to achieve certain lower ICURs (Table 9).

TABLE 9: PRICE ANALYSES FOR ONABOTULINUMTOXINA

Scenario	ICUR Based on Manufacturer's Analysis	Revised ICUR Based on CDR "Most Likely Scenario"
Manufacturer's base case	$34,029[a]	$59,388[a]
10% price reduction	$32,632	$56,918
20% price reduction	$31,234	$54,447
30% price reduction	$29,836	$51,977
40% price reduction	$28,439	$49,507
50% price reduction	$27,041	$47,036
60% price reduction	$25,644	$44,566
70% price reduction	$24,246	$42,096
80% price reduction	$22,848	$39,625
90% price reduction	$21,451	$37,155

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio.
[a] Manufacturer's submitted price of $357.00 per 100 U vial.

4. DISCUSSION

The key limitations of the manufacturer's submitted economic evaluation pertains to the use of different utility values between treatment groups within the same health state, which does not respect good modelling practices and might have introduced double-counting of potential benefits of Ona A compared with BSC. The decision to use different utility values was based on clinical trial results showing improved quality of life in Ona A patients versus BSC patients. The manufacturer attributed these findings to Ona A treatment, conferring additional benefits to patients in terms of micturition and nocturia. The same utility value should be applied to both treatment groups in a given health state. Further, it is important to note that for some health states, the difference in utility value between the two treatment groups was very small; thus, differences observed in the clinical trial might be due to the small number of patients in these health states. For the health state "< 50% reduction and ≤ 1 UIE," patients in the BSC group showed a higher utility value than patients in the Ona A group (0.852 versus 0.828), which is inconsistent with the manufacturer's justification. CDR reanalyses therefore assigned health state–specific utility values, regardless of treatment group or model cycle.

In defining the model health states, the manufacturer utilized both the absolute number of UIE and the relative reduction of UIE from baseline. The manufacturer states that integrating the absolute number of UIE as a component of the health states allows for a more straightforward association of resource use parameters with the number of UI episodes from cross-sectional studies and provides information about disease severity as defined by number of UIE. However, within the same health state, a lower number of UIEs are applied to patients on Ona A compared with patients on standard of care, thus pre-emptively overestimating the benefits of Ona A. The impact of this approach (of combining absolute and relative UIE per health state) was not relevant to this analysis, as the number of UIEs is used only in calculating the costs associated with use of incontinence pads — costs that are not normally reimbursed by Canadian drug plans.

The manufacturer acknowledged that in real life, a proportion of patients would likely continue to receive anticholinergics. The manufacturer's report indicates that the placebo effects (BSC group) from the phase 3 trials were assumed to be reflective of the treatment effects of anticholinergic medications in this patient population (i.e., patients not adequately managed with anticholinergic medications); therefore, in a conservative approach, no costs were assigned to anticholinergic medication use. However, there is evidence showing that in patients who have failed previous anticholinergic therapies, re-treatment with another anticholinergic might result in a better response than placebo only over 12 weeks.[3]

Finally, the manufacturer's sensitivity analyses showed the model results to be sensitive to variations in re-treatment frequency. The eight-month interval used by the manufacturer, based on data from the ongoing extension trial (study 096), was deemed realistic by the clinical expert despite being different from the 24-week (six-month) median interval reported in the clinical trials.

Table 10 provides a further summary of other limitations identified with the manufacturer's submission.

TABLE 10: OTHER LIMITATIONS OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Parameter/Assumption	Issue	Impact
Long-term efficacy	Extrapolation of treatment effects to five years beyond clinical trial duration (2 years in extension trial 191622-096)	Unclear: No data are available indicating if a ceiling effect or resistance might occur over time, or whether more frequent injections might be required
Re-treatment frequency assumed to occur every 8 mo	Results are sensitive to variations in re-treatment frequency. Using a 5.45-mo interval led to an ICUR of $49,071 per QALY	Re-treatment frequency might vary widely, depending on resources. Based on the clinical expert feedback, 8 mo was a realistic estimate of what could be expected

ICUR = incremental cost-utility ratio; mo = months; QALY = quality-adjusted life-year.

4.1 Issues for Consideration

4.1.1 Clinical Practice

The manufacturer's requested listing for Ona A is for the treatment of refractory UI due to overactive bladder; Canadian clinical guidelines suggest that patients may be considered refractory if they have tried and failed at least two adequate trials of anticholinergic medications.[11] Myrbetriq (mirabegron), a drug from a different class of treatments (i.e., selective beta 3-adrenoceptor agonist), received approval by Health Canada for the treatment of OAB with symptoms of urgency, urgency incontinence, and urinary frequency, and is currently under review by CDR. The impact of mirabegron's introduction on the place of Ona A in the treatment of OAB in Canada and the consequent utilization of SNS is unclear. The cost-effectiveness of Ona A compared with mirabegron is also unclear at this time.

Other Health Technology Assessment Findings

Ona A has received positive recommendation from the Scottish Medicines Consortium and the Australian Pharmaceutical Benefits Advisory Committee for this indication. Further information pertaining to these recommendations is located in Appendix 4.

4.2 Off-label or Expanded Use

Clinical expert opinion defined response to Ona A therapy as a 50% improvement in OAB symptoms, not exclusive to UI; improvement in urgency episodes, reduction in frequency, or improvement in nocturia (i.e., being able to defer two hours before micturition versus hourly). The expanded definition of treatment response suggests a possible increase in Ona A utilization in patients who may be showing less than 50% reduction in their daily incontinence episodes but are considered positive responders due to improvements in other symptoms.

4.3 Patient Input

Patient input was received from The Canadian Continence Foundation (TCCF), which compiled information through a cross-sectional survey of a random cohort of Canadian patients with OAB currently receiving treatment, who were initially identified from the Foundation's database. The patient group stated that patients with OAB experience:

- Negative effects on social life through the inability to leave home as often as desired, avoiding going out on holidays, avoiding public transportation, fear of odour, reduction in sexual activity, and avoidance of new intimate relationships
- Reduced ability to work or loss of productivity
- Financial burden from purchasing incontinence supplies, which are not subsidized.

The economic evaluation submitted by the manufacturer takes into account the costs and outcomes associated with UIEs due to OAB. The manufacturer's submission also includes an economic analysis from the societal perspective as part of the sensitivity analyses. The societal perspective considers the productivity loss associated with OAB.

4.4 Conclusions

A key limitation was the manufacturer's modelling of health state utilities. Other limitations include the stopping rule for Ona A, proportion of patients receiving SNS, time to initiation of SNS, and efficacy of anticholinergics in the BSC group compared with real-life clinical practice. When accounting for these limitations, CDR found that the ICUR of Ona A plus BSC compared with BSC alone ranged from $56,932 to $60,451 per QALY gained, with a most likely ICUR estimate of $59,388 per QALY gained. The place in therapy and cost-effectiveness of Ona A compared with mirabegron is unclear at this time.

APPENDIX 1: COST COMPARISON TABLE

Clinical experts have deemed the comparators presented in Table 11 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 11: COST COMPARISON TABLE FOR OVERACTIVE BLADDER

Drug/Comparator	Strength	Dosage Form	Price ($)[a]	Recommended Dose	Average Daily Drug Cost ($)	Annual Drug Cost ($)
Ona A (Botox)	**50 units 100 units 200 units**	**Vial**	**178.5000[b] 357.0000[b] 714.0000[b]**	**100 units/dose Every 3 mo Every 24 weeks**	** 3.91 2.12**	** 1,428 776**
Fesoterodine fumarate (Toviaz)	4 mg 8 mg	ER tab	1.5000	4 to 8 mg daily	1.50	548
Darifenacin (Enablex)	7.5 mg 15 mg	ER tab	1.5800	initial dose 7.5 mg daily; final dose 7.5 mg to 15 mg daily	1.58	577
Mirabegron (Myrbetriq)	25 mg 50 mg	ER tab	1.7400[c]	25 to 50 mg once daily	1.74	635
Oxybutynin chloride (Generics)	5 mg	tab	0.0986	5 mg 2 to 3 times daily	0.20 to 0.30	72 to 108
Oxybutynin (Oxytrol)	36 mg	TD patch	7.3188[d]	one patch twice weekly	2.09	763
Oxybutynin chloride (Gelnique)	100 mg/g	topical gel	3.0380[d]	one 1 g sachet daily	3.04	1,109
Oxybutynin chloride ER (Ditropan XL)	5 mg 10 mg	ER tab	2.4717[d]	5 to 30 mg daily	2.47 to 7.42	902 to 2,707
Oxybutynin chloride (Uromax)	10 mg 15 mg	CR tab	1.4816[d] 1.5961[d]	10 to 20 mg daily	1.48 to 2.96	571 to 1,082
Solifenacin succinate (Vesicare)	5 mg 10 mg	tab	1.6400	5 to 10 mg daily	1.64	599
Tolterodine (Detrol LA)	2 mg 4 mg	ER-cap	1.9466	4 mg daily	1.95	711
Tolterodine (Detrol)	1 mg 2 mg	tab	0.9733 0.9733	2 mg twice daily	1.95	711
Trospium chloride (Trosec)	20 mg	tab	0.7905	20 mg twice daily	1.58	577

cap = capsule; CDR = CADTH Common Drug Review; CR = controlled release; ER = extended release; mo = months; ODB = Ontario Drug Benefit Formulary; Ona A = onabotulinumtoxinA; tab = tablet; TD = transdermal.

[a] Unless otherwise indicated, all prices are from the Ontario Drug Benefit Formulary (accessed August 2014) and do not include dispensing fees.

[b] Manufacturer's submitted price and ODB list price; dose frequency based on product monograph maximum of every 3 months and monograph-reported clinical trial median of every 24 weeks.

[c] PPS Buyer's Guide (January 2014). Myrbetriq is currently under review by CDR for overactive bladder.

[d] McKesson Canada wholesale price (June 2014).

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 12: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS ONABOTULINUMTOXINA RELATIVE TO BEST SUPPORTIVE CARE?

Ona A Versus Best Supportive Care	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	Manufacturer's base case: $34,029 per QALY gained					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 13: 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 uncertainty about the health state utilities		
Was the material included (content) sufficient?	X		
Comments			
Was the submission well organized and was information easy to locate?	X		
Comments			

TABLE 14: AUTHOR INFORMATION

Authors	Affiliations
Kristin Khalaf Daisy Ng-Mak Gordon Petrovic Beth Koster	Allergan Inc.
Sanja Stanisic Dmitry Gultayev Johanna Lister	LASER ANALYTICA

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis	X		

APPENDIX 4: OTHER HEALTH TECHNOLOGY ASSESSMENT FINDINGS

Two health technology assessment (HTA) bodies have published recommendations regarding onabotulinumtoxinA (Ona A) in this indication: the Scottish Medicines Consortium[12] and the Australian Pharmaceutical Benefits Advisory Committee.[13] A summary of these recommendations is provided in Table 15.

TABLE 15: OTHER HEALTH TECHNOLOGY ASSESSMENT FINDINGS

	SMC (June 2014)[12]	PBAC (Nov 2013)[13]
Drug	OnabotulinumtoxinA (Botox)	
Price	£276 to £552 per year C$505 to C$1,009 per year	Not reported
Treatment	OnabotulinumtoxinA (100 units)	
Comparator	BSC: behavioural therapy and incontinence pads with option of anticholinergics and CIC	BSC: lifestyle management, physiotherapy, incontinence pads
Population modelled	Patients with bladder dysfunction who are not adequately managed with anticholinergics and OAB with symptoms of UI, urgency, and frequency	Patients with idiopathic overactive bladder incontinence
Time horizon	10 years	
Discount rate	Not reported	
Study question	Not reported	
Type of model	Cost-utility model	
Key outcomes	ICERs, QALYs	ICERs, QALYs
Results	• Base case: dominant, savings of £469 and QALY gain of 0.342	• Base case: Dominant • Most conservative multivariate SA: ICER = A$15,000 to A$45,000/QALY
Sources of uncertainty	Patient outcomes and costs with BSC, particularly pads, adverse events	Health state utility values, costs of pads, non-inclusion of applicable costs, adverse events
CDR assessment	• Efficacy and safety data appear to be obtained from same clinical trials as in CDR submission • Results are different from CDR primarily due to differences between Canada and other countries in terms of reimbursement and costing practices (e.g., incontinence pad for OAB are reimbursed in Scotland) • Definition of health states differed between SMC and CDR submissions; in SMC submission, the health states were based on number of daily UIEs. In the SMC submission, the health states were: dry, > 0 to ≤ 2 UI episodes, > 2 to < 5 UI episodes, ≥ 5 UI episodes and death • Economic modelling approach in CDR submission appears to be different from those submitted to other countries; e.g., longer time horizon, disutility associated with UTIs, and treatment benefits from continued use of anticholinergic medications	

A$ = Australian dollars; BSC = best supportive care; C$ = Canadian dollars; CDR = CADTH Common Drug Review; CIC = clean intermittent catheterization; ICER = incremental cost-effectiveness ratio; OAB = overactive bladder; PBAC = Pharmaceutical Benefits Advisory Committee; QALY = quality-adjusted life-year; SA = sensitivity analysis; SMC = Scottish Medicines Consortium; UI = urinary incontinence; UIE = urinary-incontinence episodes; UTI = urinary tract infection.
£1.00 ≈ C$1.8286; A$1.00 ≈ C$1.0006 (Bank of Canada, July 9, 2014).

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