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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

abobotulinumtoxinA (Dysport Therapeutic)

(Ipsen Biopharmaceuticals Canada, Inc.)

Indication: For the symptomatic treatment of lower-limb spasticity in pediatric patients 2 years of age and older

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Abbreviations

aboBoNTA	abobotulinumtoxinA
CDR	CADTH Common Drug Review
EQ-5D	EuroQol 5-Dimensions questionnaire
GAS	goal attainment scaling
ICUR	incremental cost-utility ratio
LLS	lower-limb spasticity
MAS	Modified Ashworth Scale
NMA	network meta-analysis
onaBoNTA	onabotulinumtoxinA
QALY	quality-adjusted life-year
SOC	standard of care

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	aboBoNTA
Study Question	What is the cost-effectiveness of aboBoNTA compared with onaBoNTA for the treatment of pediatric patients with LLS from a provincial ministry of health perspective?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Pediatric patients two years of age or older with LLS
Treatment	AboBoNTA 10 U/kg to 15 U/kg per leg
Outcome	QALYs
Comparator	OnaBoNTA 6 U/kg per leg
Perspective	Canadian public health care payer
Time Horizon	12.2 years
Results for Base Case	ICUR = $7,117 per QALY gained.
Key Limitations	• The manufacturer's use of the GAS outcome to determine response was not well justified and is of questionable clinical appropriateness. • The manufacturer's base case assumed the efficacy of onaBoNTA was equivalent to placebo, which CDR did not consider appropriate, based on the available information. • Several limitations were identified with the manufacturer-submitted NMA that was used to inform the results of a scenario analysis. The limitations identified led CDR clinical reviewers to conclude that the relative effects of aboBoNTA versus onaBoNTA and placebo for all outcomes are uncertain. Clinical expert feedback indicated the treatments are likely to have similar efficacy and safety. • The response rate for aboBoNTA was indicated to be based on the total number of responders observed in Study 141 [redacted]. However, this combined response rate did not appear to consider variation in response rate by dosage, and the manufacturer did not provide adequate information on how the subgroup of patients was chosen. • The uncertainty around input parameters was not represented by statistical distributions but assumed to be 5% or 20% of their mean values without justification. • No analysis was undertaken comparing aboBoNTA with SOC (non-BoNTA treatments).
CDR Estimate(s)	• There was substantial uncertainty in the CDR estimates due to the quality of the evidence comparing the safety and efficacy of aboBoNTA and onaBoNTA, which precluded the CDR clinical reviewers from being able to reach a conclusion regarding the comparative efficacy and safety of aboBoNTA and onaBoNTA. Feedback from the clinical experts consulted by CDR suggested the treatments are likely similar. • If the efficacy of aboBoNTA and onaBoNTA are considered equivalent, aboBoNTA is as effective but more expensive than onaBoNTA, based on the results of the CDR reanalysis. A price reduction of approximately 5% is required for aboBoNTA to be less costly than onaBoNTA for pediatric patients with LLS. • CDR undertook a scenario analysis comparing aboBoNTA with SOC based on the data from Study 141, which resulted in an ICUR of $335,318 per QALY. A price reduction of 75% indicated that the ICUR was approximately $85,000 per QALY.

aboBoNTA = abobotulinumtoxinA; CDR = CADTH Common Drug Review; GAS = goal attainment scaling; ICUR = Incremental cost-utility ratio; LLS = lower-limb spasticity; NMA = network meta-analysis; onaBoNTA = onabotulinumtoxinA; QALY = quality-adjusted life year; SOC = standard of care; U = units.

Drug	AbobotulinumtoxinA (Dysport Therapeutic)
Indication	For the symptomatic treatment of lower-limb spasticity in pediatric patients 2 years of age and older
Reimbursement Request	As per indication
Dosage Form	Sterile lyophilized powder for solution for injection, 300 U and 500 U per vial
NOC Date	December 21, 2017
Manufacturer	Ipsen Biopharmaceuticals Canada, Inc.

Executive Summary

Background

AbobotulinumtoxinA (aboBoNTA) is a botulinum toxin that blocks nerve activity in the muscles, causing a temporary reduction in muscle activity. The recommended starting dosage of aboBoNTA for pediatric patients with lower-limb spasticity (LLS) is 10 U/kg to 15 U/kg for unilateral lower-limb injections, or 20 U/kg to 30 U/kg for bilateral lower-limb injections per treatment session. Treatment can be administered to multiple sites of muscles within the lower limb. If the treatment effect from the first dose diminishes over time, patients can be re-treated after a period of at least 12 weeks.

The manufacturer submitted a cost-utility analysis comparing aboBoNTA with onabotulinumtoxinA (onaBoNTA) in pediatric patients two years of age or older with unilateral or bilateral LLS. The base-case analysis was conducted from the perspective of the Canadian health care system over a 12-year time horizon with future costs and benefits discounted at 1.5%. The model consisted of five health states (response — on treatment; response — discontinued; non-response — on treatment; non-response — discontinued; and death) with patients transitioning between health states every 12 weeks. Response was determined based on goal attainment scaling (GAS) scores (measured as a calculated T score). For patients receiving aboBoNTA, results from Study 141 were used to inform the response rate and health-state transitions for each 12-week cycle. For patients receiving onaBoNTA, the manufacturer considered multiple analyses because there are no studies that directly compare the efficacy of aboBoNTA and onaBoNTA. Although the manufacturer provided a network meta-analysis (NMA) to support the review, in the base-case analysis the response rate and transitions for onaBoNTA patients were assumed to be equal to the response rate observed at 12 weeks in patients receiving placebo in Study 141. The manufacturer reported that the onaBoNTA studies did not measure GAS in the same manner as the aboBoNTA trials (absolute change as opposed to percentage change), leading to uncertainty with the NMA results. Scenario analyses were undertaken using response rates obtained from the onaBoNTA arm of the manufacturer-sponsored NMA and the Bjornson et al. study. Utility data were derived by transforming the data obtained from the general health-related quality-of-life questionnaire (Pediatric Quality of Life Inventory [PedsQL]) utilized in Study 141 to EuroQol 5-Dimensions questionnaire (EQ-5D) data. Utility values depended on the response status defined by GAS. Resource use was obtained from a Canadian survey of multidisciplinary clinicians, while unit costs were retrieved from the Ontario Drug Benefit Formulary, the Ontario Schedule of Benefits, and the Canadian

Institute for Health Information case mix. The manufacturer assumed approximately 33% of patients in each treatment group were receiving baclofen. Drug wastage was included in the base case.

The manufacturer reported that aboBoNTA was associated with 0.10 quality-adjusted life-years (QALYs) gained and an additional $736 compared with onaBoNTA, yielding an incremental cost-utility ratio (ICUR) of $7,117 per QALY.

Summary of Identified Limitations and Key Results

The CADTH Common Drug Review (CDR) identified several key limitations related to the manufacturer's model.

Firstly, the manufacturer assessed efficacy based on the GAS score, which is one of many measures of functional assessment of patients with LLS. The choice of GAS to define treatment response status was not well justified. Feedback from clinical experts consulted by CDR indicated that GAS is subjective and not a preferred measure of impairment or function, and the Modified Ashworth Scale (MAS) or Tardieu Scale are preferred measures for assessing response in patients with LLS.

Secondly, the manufacturer assumed that the efficacy of onaBoNTA was equal to the efficacy of placebo observed in Study 141. This assumption was made based on the GAS results of a study of onaBoNTA compared with placebo that indicated there was no statistically significant difference between onaBoNTA and placebo. CDR did not consider this approach appropriate due to the small sample size (N = 33) and that GAS was assessed as a measure of satisfaction and not as a primary or secondary outcome; onaBoNTA was statistically significantly different than placebo based on the primary outcomes assessed (Spasticity Measurement System and Gross Motor Function Measure).

[redacted]

Additionally, CDR noted the long-term efficacy of aboBoNTA and onaBoNTA is unknown, due to the short-term nature of the studies. In the manufacturer's base case, aboBoNTA response was assumed to remain constant after 48 weeks, based on response data from weeks 36 to 48 from Study 141; the onaBoNTA response rate beyond 12 weeks was assumed to remain constant until the end of the time horizon, i.e., approximately 12 years, based on the 12-week double-blind phase of Study 141. Given the assumption of improved response compared with onaBoNTA, and the lack of appropriate comparative data, the assumptions regarding long-term efficacy likely overestimate the comparative effect of aboBoNTA and increase the uncertainty in the manufacturer's ICUR estimates.

Furthermore, CDR was unable to validate the response rate for aboBoNTA. The manufacturer stated this was based on pooled individual responder and nonresponder data from Study 141; however, the manufacturer did not provide adequate information on the subgroup of patients for which individual patient data were used, considering 158 patients participated in Study 141. CDR also noted that adjusted GAS scores were higher in patients receiving aboBoNTA 10 U/kg/leg (GAS =) than those receiving aboBoNTA 15 U/kg/leg (GAS =). Given this response variation and the lack of information provided by the manufacturer on the population their input was derived from, CDR recalculated the pooled response rate based on a weighted GAS score of and obtained the pooled response rate of .

Finally, the manufacturer did not consider standard of care (SOC) (no botulinum toxin A treatment) to be an appropriate comparator. As onaBoNTA is indicated for equinus foot deformity and not LLS, it may not be reimbursed for this condition in all CDR-participating jurisdictions across Canada. As such, CDR considered that a comparison of aboBoNTA compared with SOC should have been included.

The CDR base case considered the short- and long-term comparative effectiveness of aboBoNTA to be equivalent to onaBoNTA, with the reanalysis resulting in an incremental cost of $1,508 for aboBoNTA compared with onaBoNTA. CDR also conducted a scenario analysis of aboBoNTA compared with SOC to address the comparative efficacy of aboBoNTA with SOC in jurisdictions that do not reimburse onaBoNTA for LLS. Using the manufacturer's submitted analysis as the basis of the comparative efficacy assumptions and the revised response rate of aboBoNTA, and excluding costs associated with onaBoNTA treatment, the scenario analysis indicated that the ICUR for aboBoNTA compared with SOC was $335,318 per QALY.

Conclusions

The key limitations of this submission were the use of GAS to define response in the manufacturer's model, given the subjectivity of the measure and the uncertainty associated with the short- and long-term comparative efficacy of aboBoNTA and onaBoNTA.

CDR attempted to address the identified limitations in a revised base case. Although the comparative efficacy and safety of aboBoNTA and onaBoNTA is unknown and highly uncertain, if the assumption of equivalent clinical efficacy between aboBoNTA and onaBoNTA is accurate, aboBoNTA would be as effective as onaBoNTA but more costly. A price reduction of 5% is required for aboBoNTA to be less costly for pediatric patients with LLS, given the different weight distributions used in the model. In jurisdictions that do not reimburse onaBoNTA for LLS, aboBoNTA is associated with an ICUR of $335,318 per QALY compared with SOC. With a 75% price reduction for aboBoNTA, the ICUR is approximately $85,000 per QALY compared with SOC.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's PE Submission

The manufacturer submitted an economic model that captured health outcomes in terms of quality-adjusted life-years (QALYs) gained and life-years gained.[1] The model compared the cost-effectiveness of abobotulinumtoxinA (aboBoNTA) with onabotulinumtoxinA (onaBoNTA), the only botulinum toxin A currently reimbursed in Canada for a similar condition (equinus foot deformity). The target population was pediatric patients two years of age or older with lower-limb spasticity (LLS). The modelled patients were, on average, assumed to be approximately 5.8 years at the time of entry into the model. The average weight was 22.96 kg, and 41.4% of the population was assumed to require bilateral treatment for cerebral palsy. The model was run using a 12-week cycle over a 12.2-year time horizon. All costs and outcomes were discounted at an annual rate of 1.5%, and the analysis was conducted from the perspective of the Canadian publicly funded health care system.[1]

A cohort multi-state Markov model developed in Microsoft Excel was used to simulate the disease trajectory of pediatric patients with LLS receiving treatment with aboBoNTA or onaBoNTA based on goal attainment scaling (GAS), a method for measuring a patient's success at meeting the goals they have set as a part of receiving therapy. A composite GAS score was used to calculate an aggregated T score with a mean of 50 and a standard deviation of 10. A composite score of 50 indicates that goals are achieved at the expected level, assuming a normal distribution. Non-response corresponds to a score of 50 or less on the composite measure, while response corresponds to a composite score of more than 50. The model consisted of five health states: response — on treatment; response — discontinued; non-response — on treatment; non-response — discontinued; and death (Figure 1).[1]

Transition probabilities were obtained from Study 141 assessing the efficacy of aboBoNTA compared with placebo and Study 147 evaluating safety and efficacy of repeat aboBoNTA injection cycles. In the base case, the response rate for onaBoNTA (the comparator treatment) was assumed to be equivalent to placebo in Study 141. Health-state utilities were obtained by mapping Pediatric Quality of Life Inventory (PedsQL) results to the EuroQol 5-Dimensions questionnaire (EQ-5D) via a published algorithm. The PedsQL data were obtained from Study 141; a mixed-effects regression model was fitted to obtain utilities associated with GAS response states. The manufacturer obtained direct health care costs from publicly available sources in Ontario.[1]

The manufacturer assumed approximately 33% of patients in each treatment group were receiving baclofen. Drug wastage was included in the base case.[1]

Manufacturer's Base Case

Table 2: Summary of Results of the Manufacturer's Base Case

Treatment	Total Costs ($)	Incremental Cost ($)	Total QALYs	Incremental QALYs	Incremental Cost per QALY ($)
AboBoNTA	44,469	736	9.08	0.10	7,117
OnaBoNTA	43,733		8.98		

aboBoNTA = abobotulinumtoxinA; onaBoNTA = onabotulinumtoxinA; QALY = quality-adjusted life-year.

Source: Manufacturer's pharmacoeconomic submission.[1]

Summary of Manufacturer's Sensitivity Analyses

A series of scenario analyses was performed by varying the following parameters: relative efficacy of aboBoNTA and onaBoNTA, dosage of onaBoNTA, vial-sharing assumption, and aboBoNTA treatment interval. The results of the scenario analyses suggested the extended treatment interval for aboBoNTA, increased dosage of onaBoNTA, and incorporation of vial sharing were the top three drivers of the cost-effectiveness results.[1]

A probabilistic analysis was performed using the Monte Carlo simulations with 10,000 iterations. The results of the probabilistic analysis showed that 82.6% of the simulations fell in the northeast quadrant and 16.6% fell in the dominant southeast quadrant. The cost-effectiveness acceptability curve revealed that at a willingness to pay of $50,000 per QALY gained, the probabilities that aboBoNTA is cost-effective is 97.5%.[1]

Limitations of Manufacturer's Submission

CDR identified the following key limitations with the manufacturer's model.

- **The use of GAS to define a response status was not well justified.** In Study 141 and Study 147, the Modified Ashworth Scale (MAS) was used as the primary outcome while GAS was a secondary outcome. Feedback from Canadian clinical experts indicated that GAS is a subjective measure of determining function and they do not consider it a reliable or preferred measure to define response in clinical practice; the MAS or Tardieu Scale are considered more relevant measures to assess response in practice. As the studies indicated differences between different functional outcomes, the use of a different scale may result in variation in response rate and probabilities that patients transition between health states. CDR was unable to test the effect of this limitation because no comparative response rates based on MAS or Tardieu Scale scores for aboBoNTA and onaBoNTA were reported in a way that was usable in the economic model.
- **The comparative efficacy and safety of aboBoNTA and onaBoNTA is unknown and highly uncertain.** In the base-case analysis, the manufacturer assumed that the response rate among children receiving onaBoNTA was equal to the response rate observed in patients receiving placebo in Study 141. This assumption, that the effects of onaBoNTA are similar to placebo, was based on the results of the GAS outcome in the Bjornson et al. study assessing onaBoNTA compared with placebo,[2] which suggested no significant difference in change from baseline in GAS between onaBoNTA and placebo. CDR considered this assumption inappropriate given the small sample size (33 participants) and that the GAS was a tertiary outcome, measured alongside the

satisfaction portion of the Canadian Occupational Performance Measure to assess societal limitations and not a primary or secondary outcome. Significant differences between onaBoNTA and placebo were found in the primary end points assessed for impairment and functional limitations (Spasticity Measurement System and the Gross Motor Function Measure). [redacted]

- **The long-term comparative efficacy of aboBoNTA and onaBoNTA is unknown.** In the base case, aboBoNTA response was assumed to remain constant after the 48 weeks, based on response data from week 36 to week 48 from Study 141, while the onaBoNTA response was assumed to remain constant from week 12 until the end of the time horizon, i.e., approximately 12 years, based on the 12-week double-blind phase of Study 141. Given the assumption of improved response compared with onaBoNTA, and the lack of appropriate comparative data, the assumptions regarding long-term efficacy likely overestimate the comparative effect of aboBoNTA and increase the uncertainty in the manufacturer's ICUR estimates.
- **The uncertainty in the derivation of the aboBoNTA response rate.** In the manufacturer's base case, a response rate of [redacted] was used for aboBoNTA. The manufacturer stated this was based on individual responder and nonresponder data for both doses from Study 141 [redacted]; however, the manufacturer did not provide adequate information on the subgroup of patients for which individual patient data were used. CDR notes that the total number of patients participating in Study 141 was 158 and that the adjusted GAS scores were higher in patients receiving aboBoNTA 10 U/kg/leg (GAS = [redacted]) than in those receiving aboBoNTA 15 U/kg/leg (GAS = [redacted]). Given this response variation and the lack of information provided by the manufacturer on the population their input was derived from, CDR recalculated the pooled response rate based on a weighted GAS score of [redacted] and obtained the pooled response rate of [redacted].
- **Standard of care (SOC) was not considered a comparator for jurisdictions that do not reimburse onaBoNTA for LLS.** The manufacturer did not consider a scenario in which onaBoNTA is not available, making SOC (oral treatments for LLS) an appropriate comparator. As onaBoNTA is indicated for equinus foot deformity and not LLS, it may not be reimbursed for this condition in all CDR-participating jurisdictions across Canada. A comparison of aboBoNTA compared with SOC should have been considered by the manufacturer.

Other limitations identified by CDR include the following:

- The proportion of children who require bilateral therapy was lower than may be expected in Canadian practice. The CDR clinical expert suggested that the proportion of children receiving bilateral treatments in actual practice would be higher than what was used in the manufacturer's model. As suggested by the CDR clinical expert, CDR increased the percentage of children with bilateral treatments to 80%.
- The uncertainty around most input parameters was assumed to be 5% or 20% of their mean values. The uncertainty observed in the probabilistic results may not fully reflect the actual uncertainty around the parameters used in the model. The manufacturer should have tested uncertainty using the statistical distributions derived from their trial data or the network meta-analysis (NMA). Where possible, CDR attempted to assess the actual parameter uncertainty by deriving standard errors from the reported 95% confidence intervals and sample size.
- It is unclear how a treatment interval would affect the ICUR results. Although the manufacturer performed the scenario analysis and showed that increasing the treatment interval from 12 to 16 weeks caused aboBoNTA to become a cost-saving therapy. Given that the efficacy of onaBoNTA beyond 12 weeks is unknown, the results of this scenario analysis may be highly uncertain. CDR was unable to test this limitation due to the paucity of long-term comparative efficacy data.
- While the NMA-based scenario analysis was based on pooled relative efficacy regardless of treatment dose, the manufacturer's base case assumed a dose of 15 U/kg/leg. CDR noted that the pooled GAS score change from baseline obtained from two dosages of aboBoNTA was larger than the GAS score observed in aboBoNTA 15 U/kg/leg (change from baseline: 5.68 versus 4.72). The use of pooled GAS scores to define response to treatment may underestimate the ICUR of aboBoNTA. CDR assessed this difference in a scenario analysis.

CADTH Common Drug Review Reanalyses

Based on the aforementioned limitations identified, CDR undertook a revised base-case analysis with the following revisions:

- the weighted 12-week response rate of aboBoNTA was recalculated (i.e., replacing 59.18% with 54.73%)
- both the short-term (≤ 48 weeks) and long-term (> 48 weeks) efficacy of onaBoNTA was assumed to be equal to AboBoNTA
- the standard error was derived from the reported 95% CI of GAS score as opposed to assuming a standard error of 5% of the response rate (manufacturer's base case)
- the percentage of children who required bilateral therapy was increased to 80%.

CDR also undertook scenario analyses on the CDR base case testing revised discontinuation rates (5% and 15%), an increased treatment interval (16 and 22 weeks), and using the response rate of aboBoNTA 15 U/kg instead of the response rate of the pooled dose (10 U/kg/leg and 15 U/kg/leg) (Table 14).

CDR's revised base case (Table 3) showed that aboBoNTA was as effective as and more costly than onaBoNTA. Results of the Monte Carlo simulations showed that aboBoNTA was dominated (more expensive with equal QALYs gained) in 97.9% of 10,000 iterations. The results of CDR reanalyses suggested that the cost-effectiveness of aboBoNTA was highly

sensitive to the assumption regarding the short- and long-term comparative efficacy of aboBoNTA and onaBoNTA treatment interval and discontinuation rate (Table 14).

Table 3: CDR Revised Base Case

	Total Costs ($)	Incremental Cost ($)	Total QALYs	Incremental QALYs	Incremental Cost per QALY ($)
AboBoNTA	47,998	1,508	9.07	0.00	AboBoNTA is more costly
OnaBoNTA	46,491		9.07		

aboBoNTA = abobotulinumtoxinA; CDR = CADTH Common Drug Review; onaBoNTA = onabotulinumtoxinA; QALY = quality-adjusted life-year.

CDR undertook a scenario analysis to consider the cost-effectiveness of aboBoNTA in CDR-participating jurisdictions that do not reimburse onaBoNTA for LLS. The analysis was undertaken using the manufacturer's base-case analysis, with revised assumptions as per the CDR base case; although the response rate based on placebo from Study 141 was maintained and all costs associated with onaBoNTA (drug and administration) were set to zero. As per the manufacturer's base case, 33% of patients received oral treatments. The results indicated that the ICUR for aboBoNTA compared with SOC was $335,318 per QALY (Table 4). At a willingness to pay of $50,000 per QALY, the probability that aboBoNTA is cost-effective was less than 1%.

Table 4: CDR Scenario Analysis

	Total Costs ($)	Incremental Cost ($)	Total QALYs	Incremental QALYs	Incremental Cost per QALY ($)
AboBoNTA	48,124	34,837	9.08	0.10	335,318
SOC	13,287		8.97		

aboBoNTA = abobotulinumtoxinA; CDR = CADTH Common Drug Review; QALY = quality-adjusted life-year; SOC = standard of care.

CDR undertook a price reduction analysis based on the manufacturer's and CDR's revised base case. The price reduction scenario based on CDR's revised base case showed that aboBoNTA would become a less costly treatment than onaBoNTA if the drug cost of aboBoNTA was reduced by 5%. The price-reduction scenarios based on the CDR scenario analysis indicated that with a 75% price reduction for aboBoNTA, the ICUR was approximately $85,000 per QALY compared with SOC (Table 5).

Table 5: CDR Reanalysis Price-Reduction Scenarios Based on the CDR Base Case

ICURs of AboBoNTA			
Price	**Manufacturer's Base Case**	**CDR Base Case**	**CDR Scenario Analysis**
Submitted	$7,117 per QALY vs. onaBoNTA	AboBoNTA is as effective and $1,508 more costly	$335,318 per QALY vs. SOC
5% reduction	AboBoNTA is dominant	AboBoNTA is $219 less costly	NA
50% reduction	AboBoNTA is dominant	AboBoNTA is less costly	$168,292 per QALY vs. SOC
75% reduction	AboBoNTA is dominant	AboBoNTA is less costly	$85,014 per QALY vs. SOC

aboBoNTA = abobotulinumtoxinA; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; NA = not assessed; onaBoNTA = onabotulinumtoxinA; QALY = quality-adjusted life-year; SOC = standard of care; vs. = versus.

Issues for Consideration

- The clinical experts consulted by CDR indicated that the study population enrolled into Studies 141 and 147 had mild symptoms, which makes it difficult to generalize the cost-effectiveness results to patients with advanced disease.
- Although the costs of botulinum toxin therapy vary by weight, the submitted model assumes no vial sharing, which is appropriate based on the feedback from the clinical experts consulted by CDR.

Patient Input

Patient groups reported that patients had used onaBoNTA and oral therapies to treat their spasticity symptoms as well as other non-pharmacologic treatments (e.g., physiotherapy, occupational therapy). OnaBoNTA was reported to reduce spasticity; improve stretching, positioning, range of motion, and gait patterns; decrease stiff muscle pain and improve tolerance of leg braces; allow greater independence; and improve the ability of patients to personally care for themselves. However, upon receiving onaBoNTA, patients still require intensive physiotherapy. Some adverse events were reported (e.g., injection site pain), and patients noted travel and access issues as well as financial challenges associated with using onaBoNTA. Patient groups reported that patients would like treatments with longer-lasting effects that reduce muscle spasticity and tone and allow participation in more social and recreational activities. Given the subjectivity of the outcome used in the economic model (GAS), it is uncertain whether the unmet needs identified by the patient groups were adequately addressed.

Conclusions

The key limitations of this submission were the use of GAS to define response in the manufacturer's model, given the subjectivity of the measure and the uncertainty associated with the short- and long-term comparative efficacy of aboBoNTA and onaBoNTA.

CDR attempted to address the identified limitations in a revised base case. Although the comparative efficacy and safety of aboBoNTA and onaBoNTA is unknown and highly uncertain, if the assumption of equivalent clinical efficacy and safety between aboBoNTA and onaBoNTA is accurate, aboBoNTA would be as effective as onaBoNTA but more costly. A price reduction of 5% is required for aboBoNTA to be less costly for pediatric patients with LLS, given the different weight distributions used in the model. In jurisdictions that do not reimburse onaBoNTA for LLS, aboBoNTA is associated with an ICUR of $335,318 per QALY compared with SOC. With a 75% price reduction for aboBoNTA, the ICUR was approximately $85,000 per QALY compared with SOC.

Appendix 1: Cost Comparison

The comparators presented in **Error! Reference source not found.** have been deemed to be appropriate by clinical experts. 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. Existing Product Listing Agreements are not reflected in the table and, as such, may not represent the actual costs to public drug plans.

Table 6: CDR Cost Comparison Table for BoNTA Treatments for Pediatric Patients with LLS

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Cost per Treatment[a]	Average Annual Drug Cost[a,b]
AbobotulinumtoxinA (Dysport Therapeutic)	300 U 500 U	Vial for injection	428.4000[c] 714.0000[c]	Total of 10 U/kg to 15 U/kg for unilateral lower-limb injections; total of 20 U/kg to 30 U/kg for bilateral. Not to exceed 15 U/kg unilateral, 30 U/kg bilateral, or 1,000 U, whichever is lower. Repeat doses should be administered when clinical effect diminishes but not more than every 12 weeks; majority of study patients were re-treated at between 16 and 22 weeks	**Unilateral** • 20 kg patient: $428 • 50 kg patient: $714 to $1,142 **Bilateral** • 20 kg patient: $714 to $857 • 50 kg patient: $1,428 • 70 kg patient: $1,428	**Unilateral** • 20 kg patient: up to $2,140 • 50 kg patient: up to $5,712 **Bilateral** • 20 kg patient: up to $4,284 • 50 kg patient: up to $7,140 • 70 kg patient: up to $7,140
OnabotulinumtoxinA (Botox)	50 U 100 U 200 U	Vial for injection	178.5000 357.0000 714.0000	A total of 4 U/kg for unilateral injections; initial dose totalling 6 U/kg for bilateral. Repeat doses should be administered when clinical effect diminishes but not more than every 3 months	**Unilateral** • 20 kg patient: $357 • 50 kg patient: $714 **Bilateral** • 20 kg patient: $536 • 50 kg patient: $1,071 • 70 kg patient: $1,428	**Unilateral** • 20 kg patient: up to $1,785 • 50 kg patient: up to $3,570 **Bilateral** • 20 kg patient: up to $2,678 • 50 kg patient: up to $5,355 • 70 kg patient: up to $7,140

BoNTA = botulinum toxin A; CDR = CADTH Common Drug Review; LLS = lower-limb spasticity.
Note: All prices are from the Ontario Drug Benefit Formulary (accessed May 2018)[4] unless otherwise indicated and do not include dispensing fees. Recommended doses are based on product monographs.
[a] Cost per treatment includes wastage of excess medication in vials.
[b] Annual drug cost assumes initial dose and subsequent treatments at weeks 12, 24, 36, and 48.
[c] Manufacturer's submitted price.[5]

Table 7: CDR Cost Comparison Table for Oral Treatments for Pediatric Patients with LLS

Drug / Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Cost ($)	Average Annual[b] Drug Cost[a]
Baclofen	10 mg 20 mg	Tablet	0.1595 0.3104	For adults: Initially 15 mg in 3 divided doses, increasing by 5 mg t.i.d. every 3 days to a maximum of 20 mg q.i.d. Usual dose 40 mg to 80 mg daily. Feedback from clinical experts noted the dose in children is approximately 40 mg daily	0.62	$227
Dantrolene	25 mg	Capsule	0.4000	Children age 5 to 18 years: 0.5 mg/kg once daily initially, increase as needed to 0.5 mg/kg t.i.d. or q.i.d. for 1 week, then by 0.5 mg/kg increments to as high as 3 mg/kg q.i.d., not to exceed 100 mg q.i.d. Usual dose: 2 mg/kg t.i.d.	• 20 kg patient: 1.80 • 50 kg patient: 4.80 • 70 kg patient: up to 6.40	• 20 kg patient: $657 • 50 kg patient: $1,752 • 50 kg patient: up to $2,336

CDR = CADTH Common Drug Review; LLS = lower-limb spasticity; q.i.d. = four times daily; t.i.d. = three times daily.
Note: All prices are from the Ontario Drug Benefit Formulary (accessed May 2018)[4] unless otherwise indicated and do not include dispensing fees.
Recommended dose based on product monographs and RxTx (formerly e-Therapeutics) unless otherwise stated.

Appendix 2: Summary of Key Outcomes

Table 8: When Considering Only Costs, Outcomes, & Quality of Life, How Attractive is AboBoNTA Relative to OnaBoNTA?

AboBoNTA Versus OnaBoNTA	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	N/A
Costs (total)				X		
Drug treatment costs alone				X		
Clinical outcomes						X (unknown)
Quality of life			X			
Incremental CE ratio or net benefit calculation	From the perspective of the Canadian publicly funded health care system, aboBoNTA was more expensive but provided similar QALY gained to onaBoNTA.					

aboBoNTA = abobotulinumtoxinA; CDR = CADTH Common Drug Review; CE = cost-effectiveness; N/A = not applicable; onaBoNTA = onabotulinumtoxinA; QALY = quality-adjusted life-year.
Note: Based on CDR reanalysis.

Appendix 3: Additional Information

Table 9: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments	None		
Was the material included (content) sufficient?		X	
Comments	None		
Was the submission well organized and was information easy to locate?		X	
Comments	None		

Table 10: Authors Information

Authors of the Pharmacoeconomic Evaluation Submitted to CDR
☐ Adaptation of Global model/Canadian model done by the manufacturer
☒ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer
☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer
☐ Other (please specify)

	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: Summary of Other HTA Reviews of Drug

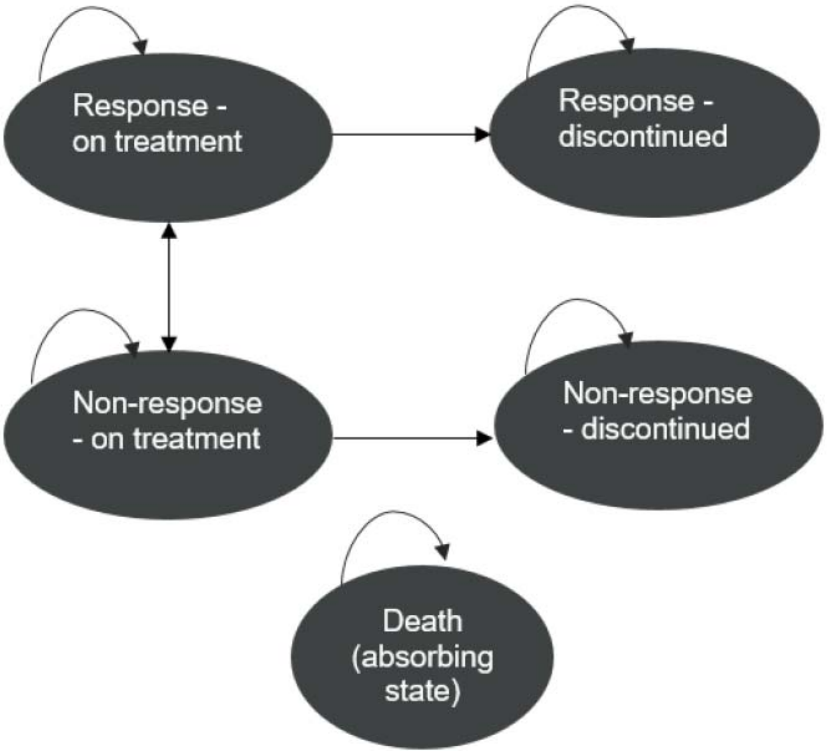
No other health technology assessment (HTA) agencies have reviewed abobotulinumtoxinA (aboBoNTA) for lower-limb spasticity in pediatric patients. AbobotulinumtoxinA has been reviewed by the Australian Pharmaceutical Benefits Advisory Committee (PBAC) for the indications of blepharospasm and hemifacial spasm in adults,[6] as well as moderate to severe spasticity of the upper limb in adults following a stroke.[7] The Scottish Medical Consortium (SMC) has reviewed aboBoNTA for focal spasticity of the upper limb associated with stroke.[8] Quebec's Institut national d'excellence en santé et en services sociaux (INESSS) has reviewed aboBoNTA for cervical dystonia[9] and upper-limb spasticity.[10]

Appendix 5: Reviewer Worksheets

Manufacturer's Model Structure

The manufacturer submitted a cohort-based Markov health state–transition model that included five health states: response — on treatment; response — discontinued; non-response — on treatment; non-response — discontinued; and death (Figure 1). After receiving an initial therapy for 12 weeks, patients are classified as either a responder or nonresponder, as defined by goal attainment scaling (GAS) score. Following this 12-week interval, patients may remain in their current response state, transition from non-response to response, or transition from response to non-response. The model assumed that 10% of patients may discontinue therapy. At any point, patients could transition to death, as informed by Canadian age- and sex-specific population mortality, adjusted by cerebral palsy–specific mortality multipliers (hazard ratio [HR] = 3.68 in males and 4.99 in females).

Figure 1: Markov Model Structure



Source: Manufacturer's pharmacoeconomic submission.[1]

Table 11: Data Sources

Data Input	Description of Data Source	Comment
Efficacy	Effect of aboBoNTA on GAS was based on Study 141[11] and 147.[12] In the base case, the effect of onaBoNTA on GAS was assumed to be equal to the effect of placebo observed in Study 141[11] based on the GAS results of a placebo-controlled onaBoNTA study (Bjornson et al.).[2] A manufacturer-sponsored NMA was also used in a scenario analysis.[3]	In Study 141 and 147, GAS was considered one of the secondary outcomes. In addition, a cut-off in GAS score of 50 was used to define response without justification. The clinical experts consulted by CDR noted that the Tardieu Scale or MAS would have been preferred measures to determine response. • The manufacturer's assumption that the response rate for onaBoNTA would be equal to the rate in the placebo arm of Study 141 was inappropriate, as it may underestimate the efficacy of onaBoNTA and inflate the relative benefit of aboBoNTA. The manufacturer claimed that the equivalence of onaBoNTA and placebo was supported by Bjornson et al.,[2] which suggested no significant differences in change from baseline in GAS between onaBoNTA and placebo. It should be noted that the non-significant difference might be a result of the small sample size considered in Bjornson et al., i.e., 33 participants. • The manufacturer-sponsored NMA was appraised by the CDR clinical team, which identified substantial limitations that did not allow them to draw conclusions regarding the efficacy and safety of aboBoNTA compared with onaBoNTA. • Given the quality of the comparative efficacy data, CDR made a conservative assumption by assuming equivalent efficacy between aboBoNTA and onaBoNTA.
Natural history	Health states were based on response to the therapy. Transition probabilities between response and non-response health states were estimated based on response rates, as measured by GAS. Patients who responded to the therapy were assumed to have a 30% reduction in health care utilization and a better quality of life.	• According to the CDR clinical expert, GAS is subjective and not a good measure of functioning. There is uncertainty associated with the validity of GAS as a measure of response. • Probabilities that patients transition between health states depend on the GAS cut-off used to define "response." The manufacturer used a GAS score of 50 to determine response to treatment without a clear justification.
Utilities	Health utility values were obtained by the PedsQL results mapped to the EQ-5D using a published algorithm. The difference in health utilities was assumed to be a sole result of response rates as measured by GAS.	Steps used to map GAS and EQ-5D were well described; however, it is unclear how health utilities for response and non-response were derived.
Adverse events	Adverse events were not considered in the economic model, as the incidence was low and the severity was mild.	Appropriate.
Mortality	All-cause mortality was informed by Canadian age- and sex-specific population mortality, adjusted by cerebral palsy state–specific mortality multipliers (HR = 3.68 in males and 4.99 in females).	Appropriate.
Resource use and costs		
Drug	The drug cost for aboBoNTA was provided by the manufacturer. Cost per unit was estimated by dividing cost per vial by 500. The cost of	Appropriate. Drug costs differ based on patient weight.

Data Input	Description of Data Source	Comment
	onaBoNTA was based on the Ontario Drug Benefit Formulary.[4]	
Administration	An administration cost of $40 was assumed.	No source or justification was provided.
Disease management	Resource utilization estimates were obtained from a survey of six Canadian clinicians, including pediatricians, pediatric neurologists, pediatric neurosurgeons, and orthopedic surgeons. For children who responded to toxin, the resource use was expected to decrease by 30% in the base case.[1]	One of the clinical experts consulted by CDR indicated that the manufacturer may have underestimated the amount of physician and specialist visits; the clinical experts agreed that overall, the assumptions made by the manufacturer were appropriate.

aboBoNTA = abobotulinumtoxinA; CDR = CADTH Common Drug Review; EQ-5D = EuroQol 5-Dimensions questionnaire; GAS = goal attainment scaling; HR = hazard ratio; MAS = Modified Ashworth Scale; NMA = network meta-analysis; onaBoNTA = onabotulinumtoxinA; PedsQL = Pediatric Quality of Life Inventory.

Table 12: Manufacturer's Key Assumptions

Assumption	Comment
In the base case, the effect of onaBoNTA on GAS was assumed to be equal to the effect of placebo observed in Study 141.[11]	The assumption was not appropriate. Assuming the response rate for onaBoNTA to be equal to a placebo arm of Study 141 may underestimate its efficacy and inflate the relative benefit of aboBoNTA. The manufacturer claimed the equivalence of onaBoNTA and placebo was supported by Bjornson et al., which suggested no significant differences in change from baseline in GAS between onaBoNTA and placebo. It should be noted that the insignificant difference might be a result of the small sample size considered in Bjornson et al.,[2] i.e., 33 participants. The manufacturer provided an NMA, noting the limitations associated with it.[1,3] CDR clinical reviewers concluded that the comparative efficacy of aboBoNTA compared with onaBoNTA was uncertain.
Response to toxin therapies was defined based on GAS. A composite T score > 50 corresponded to response.	The CDR clinical experts suggested that GAS is a subjective function measure and not a preferred measure in practice. The MAS and Tardieu Scale were the "best" or preferred measures, followed by physician global assessment, and then GAS. There are discrepancies in reporting GAS. Studies 141 and 147 reported the GAS results using a T score, while Bjornson et al. (2007) reported mean changes in GAS score from baseline.[2] CDR did not test the impact of the alternative GAS cut-off because it is unknown which GAS cut-off is appropriate.
A time horizon of 12 years was used to reflect the baseline patient age starting at six years, as determined from Studies 141 and 147, until age 18.	This was accepted as appropriate by the CDR clinical experts.
The proportion of children who required bilateral treatment was 41.4%.	The CDR clinical experts suggested that the proportion of children with bilateral treatment was higher than 41.4%, likely ~80%. CDR considered a larger proportion of children with bilateral treatment (i.e., 80%) in the CDR reanalysis.
Transition probabilities after initial 12-week treatment with onaBoNTA were assumed to be equal to response rate at 12 weeks.	Given there is no evidence on the efficacy of onaBoNTA after 12 weeks, scenario analysis should be performed to show the cost-effectiveness results in case the equivalent efficacy between aboBoNTA and onaBoNTA was assumed after 12 weeks.
Each year, 10% of the children receiving toxin therapies will discontinue the treatment.	This was felt to be appropriate by the CDR clinical expert. CDR tested this assumption by varying the discontinuation rate to 5% and 15%.
SEs of 12-week response rate for aboBoNTA and onaBoNTA were assumed to be 5% of their mean values.	This assumption was used without any justification. Assuming a small variation in response rate may underestimate the uncertainty in the cost-effectiveness results. CDR derived SEs of aboBoNTA and onaBoNTA from Study 141.

Assumption	Comment
Response to toxin therapy led to a 30% decrease in health resource utilization by children with LLS.	Changes in the magnitude of health care use are less likely to affect the ICUR because the same level of resource utilization was applied for aboBoNTA and onaBoNTA.
All patients have access to publicly funded BoNTA therapy.	May not be appropriate, as onaBoNTA is indicated for equinus foot deformity, not LLS, in Canada.

aboBoNTA = abobotulinumtoxinA; BoNTA = botulinum toxin A; CDR = CADTH Common Drug Review; GAS = goal attainment scaling; ICUR = incremental cost-utility ratio; LLS = lower-limb spasticity; MAS = Modified Ashworth Scale; NMA = network meta-analysis; onaBoNTA = onabotulinumtoxinA; SE = standard error.

Manufacturer's Results

The results of the manufacturer's base-case analysis are reported earlier (Table 2). The manufacturer performed five scenario analyses; the results are shown in Table 13.

Table 13: Manufacturer's Scenario Analyses

Description	Incremental Cost ($)	Incremental QALYs	ICUR ($ per QALY Gained)
Manufacturer's base case	736	0.10	7,117
Scenario 1: Efficacy of onaBoNTA was derived from the NMA	−34	0.18	AboBoNTA is dominant
Scenario 2: Efficacy of onaBoNTA was obtained from the Bjornson et al. study	838	0.09	10,124
Scenario 3: Dose of onaBoNTA was increased from 6 U/kg/leg to 8 U/kg/leg	−3,144	0.10	AboBoNTA is dominant
Scenario 4: Vial sharing was considered	−1,114	0.10	AboBoNTA is dominant
Scenario 4: Treatment interval for patients receiving aboBoNTA was increased	−7,283	0.10	AboBoNTA is dominant

aboBoNTA = abobotulinumtoxinA; CDR = CADTH Common Drug Review; NMA = network meta-analysis; onaBoNTA = onabotulinumtoxinA; QALY = quality-adjusted life-year; U = units.
Source: Manufacturer's pharmacoeconomic submission.[1]

CADTH Common Drug Review Reanalyses

CDR undertook a series of scenario analyses to test the impact of various parameters, including the percentage of children requiring bilateral treatments, discontinuation rates, and treatment interval (Table 14). In the scenario analyses, CDR used 10,000 iterations to ensure that the model results are stable. The results of CDR's scenario analysis reveal that the key drivers of the cost-effectiveness of aboBoNTA included treatment interval and discontinuation rate.

Table 14: The CADTH Common Drug Review's Scenario Analyses

Description	Incremental Cost ($)	Incremental QALYs	ICUR ($ per QALY Gained)
Manufacturer's base case	736	0.10	7,117
CDR's revised base case	1,508	0.00	AboBoNTA is more costly
Discontinuation rates for both treatments were reduced to 5%	1,780	0.00	AboBoNTA is more costly
Discontinuation rates for both treatments were increased to 15%	1,298	0.00	AboBoNTA is more costly
The response rate of aboBoNTA 15 U/kg/leg was used as opposed to the pooled 10 U/kg/leg and 15 U/kg/leg rate	1,496	0.00	AboBoNTA is more costly
Treatment interval for both treatments was increased to 16 weeks	1,127	0.00	AboBoNTA is more costly
Treatment interval for both treatments was increased to 22 weeks	812	0.00	AboBoNTA is more costly

aboBoNTA = abobotulinumtoxinA; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; onaBoNTA = onabotulinumtoxinA; QALY = quality-adjusted life-year; U = unit.

Table 15: CDR Scenario Analysis Compared With Standard of Care

Description	Incremental Cost ($)	Incremental QALYs	ICUR ($ per QALY Gained)
Manufacturer's base case	736	0.10	7,117
CDR scenario analysis	34,837	0.10	335,318

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

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