CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

AbobotulinumtoxinA (Dysport Therapeutic — Ipsen Biopharmaceuticals Canada Inc.)
Indication: For the symptomatic treatment of lower limb spasticity (LLS) in pediatric patients two years of age and older.

RECOMMENDATION
The CADTH Canadian Drug Expert Committee (CDEC) recommends that abobotulinumtoxinA (aboBoNTA, Dysport Therapeutic) be reimbursed for the symptomatic treatment of LLS in pediatric patients two years of age and older, if the following condition is met:

Condition
- AboBoNTA should provide cost savings for drug plans relative to onabotulinumtoxinA (onaBoNTA, Botox) for the treatment of LLS in pediatric patients

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- AboBoNTA should provide cost savings for drug plans relative to onabotulinumtoxinA (onaBoNTA, Botox) for the treatment of LLS in pediatric patients.

Reasons for the Recommendation:

1. Study 141 (n = 241) demonstrated that aboBoNTA administered as a single dose of 15 units/kg and 10 units/kg resulted in a statistically significant improvement in the primary end point (Modified Ashworth Scale [MAS] score) in the gastrocnemius-soleus complex at the ankle joint of the most affected lower limb compared with placebo at 4 weeks (−0.49 [95% confidence interval (CI), −0.75 to −0.23; *P* = 0.0002], and −0.38 [95% CI, −0.64 to −0.13; *P* = 0.0029], respectively).
2. There were no trials that directly compared aboBoNTA with onaBoNTA in pediatric patients with LLS. An indirect treatment comparison (ITC) provided by the manufacturer suggested that aboBoNTA and onaBoNTA likely have similar treatment effects in pediatric patients with LLS. However, given the limitations of the ITC and the lack of direct comparative evidence, the comparative efficacy and safety of aboBoNTA versus onaBoNTA in the treatment of pediatric patients with LLS is uncertain. Therefore, there is no evidence to suggest that aboBoNTA has any therapeutic advantage compared with onaBoNTA in pediatric patients with LLS.
3. AboBoNTA does not address any unmet need that is not currently met by onaBoNTA (if the latter is already being reimbursed) for the treatment of pediatric patients with LLS.

Of Note:

CDEC noted that aboBoNTA is the second product in the neurotoxin type A class of botulinum neurotoxins approved for use in the lower limbs of pediatric patients and that both products have the same mechanism of action. In addition, there is no evidence that aboBoNTA would be effective in patients who have had a suboptimal response to treatment with another type of botulinum neurotoxin because patients known to be resistant to botulinum neurotoxin were excluded from Study 141. The potential for the sequential use of aboBoNTA to increase the annual drug plan cost of treating patients with LLS, and the fact that this product does not fill a therapeutic gap in the treatment of LLS, led the Committee to conclude that, in order to provide value to public drug plans, aboBoNTA should provide cost savings relative onaBoNTA.

Discussion Points:

- CDEC discussed that the Health Canada–approved indication for aboBoNTA in pediatric patients is broader than that of onaBoNTA, which is indicated for the treatment of dynamic foot equinus deformity due to spasticity in pediatric cerebral palsy patients two years of age or older. However, the clinical experts consulted for this review indicated that the difference in the indications for aboBoNTA and onaBoNTA related to the treatment of LLS in pediatric patients was inconsequential in clinical practice.
- There was no clinical trial evidence to suggest that the duration of treatment effect differs between aboBoNTA and onaBoNTA.

Background:

This resubmission for aboBoNTA is for the new Health Canada–approved indication of symptomatic treatment of LLS in pediatric patients two years of age and older. AboBoNTA is a type A botulinum neurotoxin (neuromuscular blocking agent). AboBoNTA is available as a single-use sterile lyophilized powder (300 units and 500 units per vial) for reconstitution with 0.9% Sodium Chloride Injection, USP for intramuscular use. The Health Canada–recommended dosing of aboBoNTA for pediatric patients with LLS is 10 units/kg to 15 units/kg for unilateral lower-limb injections or 20 units/kg to 30 units/kg for bilateral lower-limb injections per treatment session. With the maximum total dose of administered per treatment session not exceeding 15 units/kg for unilateral lower-limb injections or 30 units/kg for bilateral lower-limb injections or 1,000 units, whichever is lower. The total dose administered should be divided between the affected spastic muscles of the lower limb(s). When possible, the dose should be distributed across more than one injection site in any single muscle (gastrocnemius and soleus muscles). No more than 0.5 mL should be administered in any single injection site. It is also recommended that dosing in initial and sequential treatment sessions to be tailored to the individual patient based on the size, number and location of muscles involved, severity of spasticity, the presence of local muscle weakness, the patient's response to previous treatment, and/or adverse event (AE) history with botulinum toxins (BoNTs). AboBoNTA treatment should be repeated when the effect of a previous injection has diminished, but no sooner than 12 weeks after the previous injection.

Submission History:

AboBoNTA was previously reviewed for reducing subjective symptoms and objective signs of cervical dystonia (spasmodic torticollis) in adults and received a recommendation to reimburse for the previously mentioned indication in adults with or without BoNT treatment experience, with the following conditions: in a manner similar to the public plan listings for other botulinum toxin A (BoNTA) products and with a reduction in price (Notice of CDEC Final Recommendation, July 2017).

AboBoNTA was also previously reviewed for the symptomatic treatment of focal spasticity affecting the upper limbs in adults and received a recommendation to reimburse with the following criterion: Reimburse AboBoNTA in a manner similar to other BoNTA products reimbursed for the treatment of upper limb spasticity; and with the following condition: AboBoNTA should provide cost savings for drug plans relative to other BoNTA products reimbursed for the treatment of upper limbs spasticity (Notice of CDEC Final Recommendation, October 2017).

Summary of CDEC Considerations:

The Committee considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of randomized controlled trials (RCTs) of aboBoNTA, one ITC submitted by the manufacturer, and a critique of the manufacturer's pharmacoeconomic evaluation. The Committee also considered input from two clinical experts with experience in treating patients with LLS, and patient group–submitted information about outcomes and issues important to patients.

Patient Input Information:

Two patient groups responded to the call for patient input for this CDR review: the Cerebral Palsy Association in Alberta and the Multiple Sclerosis Society of Canada. Patient perspectives were obtained from surveys. The following is a summary of key information provided by the patient groups:

- Children with LLS were negatively impacted in terms of their ability to attend school, participate in extracurricular activities (such as sports or clubs), sleep, socialize (e.g., going out with friends, attending parties), be mobile, independently perform age-appropriate activities, drive a car, take care of themselves (e.g., dressing, eating, and personal/toilet care), provide care to younger siblings, maintain family relationships, and participate in recreational and/or physical activities (e.g., active play, riding a bike, etc.).
- The impact of LLS on caregivers can also be considerable. Leisure activities, socializing, and work are all often negatively affected, as the demands on personal time for both patients and caregivers are significant.

- Families and patients with cerebral palsy who are experiencing LLS would like longer-lasting treatments with longer-lasting effects, ease of access to specialists and local therapists, more intensive and frequent interventions, reduced muscle spasticity and tone, financial accommodation for travel- and specialist-related expenses, and access for First Nations groups.

- Non-pharmacological therapies such as physiotherapy and occupational therapy were reported as the most common treatments used by families with children with cerebral palsy. Botox was the most common pharmacological therapy that had been used by the cerebral palsy survey respondents. Other therapies used included baclofen, trihexyphenidyl (Artane), and carbidopa-levodopa (Sinemet). In terms of dealing specifically with LLS, the use of onaBoNTA was associated with an ease of stretching; reductions in spasticity; improvements in positioning, range of motion, and gait patterns; decreases in stiff muscle pain; increased tolerance of leg braces; greater independence; and an improved ability of the patient to personally care for themselves. Some AEs reported with the use of the pharmacologic treatments included muscle weakness, bruising, and pain near the injection site. In addition, patients and caregivers also experienced difficulties in obtaining these treatments due to travel and access issues, and some families experienced financial challenges.

Clinical Trials

The systematic review included two placebo-controlled RCTs (Study 141 and Study 701). Study 141 was a pivotal trial. Study 141 (N = 241) was a phase III, multi-centre, double-blind, prospective, randomized, placebo-controlled, single treatment–cycle study that assessed the efficacy of aboBoNTA compared with placebo in children with dynamic equinus foot deformity associated with cerebral palsy. Patients were randomized into one of three treatment groups; aboBoNTA 10 units/kg, aboBoNTA 15 units/kg, or placebo in a ratio of 1:1:1. AboBoNTA or placebo was administered by intramuscular injections into the gastrocnemius-soleus complex (GSC) of each affected lower limb. The dose of aboBoNTA administered was either 10 units/kg or 15 units/kg per affected GSC, so the total dose was 10 units/kg or 15 units/kg for unilateral injections and 20 units/kg or 30 units/kg for bilateral injections. Study 701 (N = 52) was a phase III, multi-centre, double-blind, prospective, randomized placebo-controlled study, that compared the efficacy and safety of a single administration of aboBoNTA or placebo in the treatment of pediatric dynamic equinus spasticity associated with diplegic cerebral palsy. Eligible patients were randomized to receive a single treatment of either aboBoNTA (30 units/kg) or placebo. Study medication was distributed equally between both legs by injection of the gastrocnemius muscle of each limb.

One of the main limitations of the Study 141 was that clinically relevant outcomes such as passive and active function outcomes (e.g., Tardieu Scale [TS] scores) and the health-related quality-of-life outcomes were analyzed as tertiary outcomes for exploratory purposes only and were not controlled for multiple statistical testing (i.e., increased risk of type I error). The clinical expert consulted for this review indicated that patients included in the trial appeared to be limited to ambulatory patients with mild to moderate severity cerebral palsy.

The main limitation for Study 701 is that no adjustment was made for multiple testing despite secondary end points analyses, which would increase the risk of type I (false-positive) error. Also, balance may not have been achieved across the baseline variables, suggesting randomization was not successful, which may substantially bias the study results.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following:

- MAS — The MAS is a commonly used tool for assessing the response to treatment for patients with spasticity. The score ranges from 0 to 4 points; higher scores indicate more severe spasticity. There is no evidence of the validity of the MAS in pediatric patients with spasticity and there is conflicting evidence on reliability. A minimal clinically important difference (MCID) for this outcome in the pediatric population with LLS has not been established.

- Physician's Global Assessment (PGA) — The PGA is conducted by an investigator and uses a nine-point categorical scale to assess treatment response. The score ranges from −4 to +4 (−4 = markedly worse, −3 = much worse, −2 = worse, −1 = slightly worse, 0 = no change, +1 = slightly improved, +2 = improved, +3 = much improved, and +4 = markedly improved).

- Goal attainment scaling — This is a method of integrating achievement in a number of individually set goals into a single goal attainment score (GAS). The expected-achievement target is set by the patient and their treating team and given a value of 0.

Outcomes that are less than expected are given values of −1 or −2 (the most unfavourable outcome); outcomes that are greater than expected are given values of +1 or +2 (the most favourable outcome). The originators of the GAS transformed it into a standard variable (the t score), with scores ranging from 0 to 100, a mean of 50, and a standard deviation of 10. No validity or reliability studies have been conducted in children. No MCID was identified for the GAS in pediatric patients with LLS.

- TS — The TS was developed to clinically measure spasticity by measuring the different angles of reaction when passing the muscle through stretches at different predefined velocities (V). Two parameters are used to measure the muscle spasticity, namely, the spasticity angle (X) (i.e., the difference between the angle of arrest at slow speed [V1] and the clonus or catch-and-release angle at the highest speed [V3]) and the spasticity grade (Y) (i.e., the grade for the intensity of the muscle reaction to the fastest stretch [V3], which is an ordinal variable). Larger spasticity angles correspond to more spasticity in the muscle. The spasticity is graded as follows: grade 0 = absence of spasticity as defined by a catch that is not followed by a release; grade 1 = passive movement is slowed down by mild resistance; grade 2 = passive movement (the catch and release) is transiently interrupted; grades 3 and 4 = severe spasticity; and non-rateable = a catch that is not followed by an obvious release occurring at inconsistent angles. An MCID for this outcome in the pediatric population with LLS was not identified.

- Pediatric Quality of Life Inventory (PedsQL) version 4.0 — The PedsQL is a health-related quality-of-life measure that addresses the paucity of appropriately validated and reliable instruments using the PedsQL 4.0 Generic Core Scales, which incorporates both the child and parental experience with chronic health conditions. The PedsQL uses a modular approach and incorporates both generic and disease- and symptom-specific items that are appropriate for the assessment of pediatric chronic conditions. The Generic Core Scales comprise 23 items grouped under the following modules: Physical Functioning (eight items), Emotional Functioning (five items), Social Functioning (five items), and School Functioning (five items). The Generic Core Scales are composed of both a parent-proxy report and a child self-report that assess health perceptions. The questions ask how much of a problem each item has been in the past month. A five-point Likert response scale is used across the child report (for children aged eight to 18 years) and for the corresponding parent report and includes the following responses with corresponding scores: 0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; and 4 = almost always a problem. In addition, a three-point scale (0 = not at all a problem; 2 = sometimes a problem; and 4 = a lot of a problem) is used for children aged five to seven years to simplify the scales and make them easier to use, with each of the response choices anchored to a happy or sad face on the scale. The scores are transformed linearly to a 0 to 100 scale, where 0 = 100, 1 = 75, 2 = 50, 3 = 25, and 4 = 0, with higher scores indicative of higher health-related quality of life. The PedsQL has never been evaluated in pediatric patients with LLS and, currently, no known MCID exists for the PedsQL in this population.

- Gross Motor Function Measure (GMFM) — The GMFM is an outcome measure used to evaluate change in gross motor function over time in children with varying degrees of cerebral palsy. The GMFM is a validated instrument to assess response to treatment for pediatric patients with spasticity. No MCID was identified in the literature for the GMFM with regard to pediatric patients with LLS.

- Serious adverse events (SAEs), total AEs, withdrawals due to AEs, and notable harms.

The primary outcome measure in Study 141 was the change from baseline in MAS score at week 4 in the GSC at the ankle joint of the (most) affected lower limb. In Study 701, the primary efficacy variable was functional change, as assessed by the change from baseline in overall GMFM score without walking aids or orthoses at week 4 of the study.

Efficacy

- In Study 141, at week 4, the between-group mean difference in change from baseline MAS score was statistically significant (−0.49 [95% CI, −0.75 to −0.23; *P* = 0.0002]) in the aboBoNTA 15 units/kg/leg group compared with the placebo group. Likewise, the between-group mean difference in change from baseline for the aboBoNTA 10 units/kg/leg group compared with placebo was statistically significant (−0.38 [95% CI, −0.64 to −0.13; *P* = 0.0029]).

- In Study 141, patients in both aboBoNTA treatment groups achieved a mean GAS score above 50.0, demonstrating that the overall response was better than expected. However, patients in the placebo group showed a less-than-expected response,

with a mean GAS score below 50.0. This result was statistically significant in both of the aboBoNTA treatment groups compared with placebo.

- In Study 141, at week four, compared with placebo, patients assigned to aboBoNTA had statistically significantly higher (more favourable) PGA scores, with between-treatment differences of 0.82 (95% CI, 0.50 to 1.14) and 0.77 (95% CI, 0.45 to 1.10) for aboBoNTA 10 units/kg and aboBoNTA 15 units/kg, respectively ($P < 0.0001$ for both comparisons).
- Outcomes, including the TS and PedsQL, were analyzed as tertiary outcomes for exploratory purposes only. The observed improvement in muscle tone at week 4 demonstrated by the MAS score was supported by the results of the TS, another efficacy measurement for spasticity. In the TS, the spasticity grade was reduced for both treatment groups at week 4. However, no conclusion could be derived from the TS because it was analyzed as a tertiary outcome for exploratory purposes only, and no control for multiple statistical testing was used to control for the risk of type I error. As for the PedsQL, the magnitude of reduction in all groups was negligible.
- Study 701 was a relatively small trial that failed to demonstrate statistically significant between-group differences in the GMFM overall score without walking aids or orthoses at week 4. Other functional outcomes were not controlled for multiplicity.

Harms (Safety and Tolerability)

- In Study 141, treatment-emergent adverse events (TEAEs) occurred in 63.8% of the patients in both the aboBoNTA 10 units/kg and aboBoNTA 15 units/kg groups compared with 53.2% of patients in the placebo group. The most common TEAEs were upper respiratory tract infection (7.5%, 16.3%, and 12.7% in the aboBoNTA 10 units/kg, aboBoNTA 15 units/kg and placebo groups, respectively) and nasopharyngitis (12.5%, 11.3%, and 5.1% in the aboBoNTA 10 units/kg, aboBoNTA 15 units/kg and placebo groups, respectively).
- In Study 701, at least one TEAE was reported in 39% and 50% of patients in the aboBoNTA and placebo groups, respectively. The most common TEAEs were rhinitis (15% in the aboBoNTA and placebo treatment groups), and bronchitis (15% and 12% in the aboBoNTA and placebo groups, respectively).
- In Study 141, SAEs were rarely reported (1.3%, 0%, and 5.1% in the aboBoNTA 10 units/kg, aboBoNTA 15 units/kg, and placebo groups, respectively). Only one patient in the placebo group was withdrawn from the study because of an AE. No other withdrawal due to AE was reported in Study 141.
- In Study 701, one SAE was reported in the aboBoNTA group, where the patient suffered an episode of acute bronchitis. There was no withdrawal due to an AE in either treatment arm.
- In Study 701, two patients in the aboBoNTA group reported urinary incontinence.
- No death was reported in either study.

Indirect Treatment Comparisons

In the absence of direct evidence comparing aboBoNTA with other active treatments, the manufactured submitted an ITC which suggested that aboBoNTA and onaBoNTA may have similar treatment effects in pediatric patients with LLS. Also, no statistically significant difference in AEs between the aboBoNTA, onaBoNTA, or placebo groups was reported. These results, however, are limited by the small number of studies for some outcomes, the considerable amount of heterogeneity between studies, and the large number of assumptions required to pool the data for analysis. No evidence was available regarding the difference in the duration of effect between aboBoNTA and onaBoNTA.

Cost and Cost-Effectiveness

The submitted price of aboBoNTA is $428.40 for the 300 unit and $714.00 for the 500 unit single-use vials. The recommended starting dose per treatment session is 10 units/kg to 15 units/kg for unilateral lower-limb injections or 20 units/kg to 30 units/kg for

bilateral lower-limb injections. Based on a 50 kg patient, the cost per session ranges from $714 to $1,142 for unilateral treatment to $1,428 for bilateral treatment.

The manufacturer submitted a cost-utility analysis comparing aboBoNTA with onaBoNTA in pediatric patients two years of age or older with unilateral or bilateral LLS. The 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% per annum. 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 the GAS scores from Study 141. Utility data were derived by transforming the scores from the general health-related quality-of-life measure (PedsQL) used in Study 141 into EuroQol 5-Dimensions questionnaire (EQ-5D) scores. The manufacturer reported that aboBoNTA was associated with 0.10 quality-adjusted life-years (QALYs) gained and an additional cost of $736 compared with onaBoNTA, yielding an incremental cost-utility ratio of $7,117 per QALY.

CDR identified several key limitations with the manufacturer's submitted analysis:

- The use of the GAS outcome to determine response was not well justified, and is a subjective measure of determining function and not a reliable or preferred measure to define response in clinical practice.
- The manufacturer undertook an ITC comparing aboBoNTA with onaBoNTA, although they had identified several limitations which led them to not consider these data in their base case. Based on the limitations identified, CDR concluded that the relative effects of aboBoNTA versus onaBoNTA or placebo from the ITC are uncertain for all outcomes. Clinical expert feedback indicated the treatments are likely to have similar efficacy and safety.
- The manufacturer assumed in its base case that the efficacy of onaBoNTA was equivalent to placebo, which CDR did not consider appropriate, based on the available information.
- CDR was unable to validate the response rate for aboBoNTA used in the model with data from Study 141, and the manufacturer did not provide adequate clarification on the population used to derive the response rates.
- No analysis was undertaken comparing aboBoNTA with standard of care (non-BoNTA treatments).

CDR undertook a revised base-case analysis based on: the recalculated response rate for aboBoNTA; an assumption that both the short-term (≤ 48 weeks) and long-term (> 48 weeks) efficacy of onaBoNTA is equal to aboBoNTA; the standard error derived from the reported 95% CI for the GAS score (as opposed to assuming a standard error of 5% for the response rate [manufacturer's base case]); and an increase (to 80%) in the percentage of children who required bilateral therapy. In this analysis, aboBoNTA was as effective and more costly ($1,508) than onaBoNTA over the 12-year time horizon. A price reduction of approximately 5% is required for aboBoNTA to be less costly than onaBoNTA.

CDEC Members:

Dr. James Silvius (Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

July 18, 2018 Meeting

Regrets:

One CDEC member did not attend.

Conflicts of Interest:

None