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 focal spasticity affecting the upper limbs in adults.

RECOMMENDATION:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that abobotulinumtoxinA (aboBoNTA, Dysport Therapeutic) be reimbursed for the symptomatic treatment of focal spasticity affecting the upper limbs in adults, if the following criterion and condition are met:

Criterion:
Reimburse in a manner similar to other botulinum neurotoxin A (BoNTA) products reimbursed for the treatment of upper limb spasticity (ULS).

Condition:
AboBoNTA should provide cost savings for drug plans relative to other BoNTA products reimbursed for the treatment of ULS.

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Condition:

- AboBoNTA should provide cost savings for drug plans relative to other BoNTA products reimbursed for the treatment of ULS.

Reasons for the Recommendation:

1. One randomized, placebo-controlled trial (Study 145; N = 243) demonstrated a statistically significant and clinically meaningful improvement in its primary end point (Modified Ashworth Scale [MAS] for the primary targeted muscle group [PTMG]) with a single dose of aboBoNTA 1,000 U and 500 U as compared with placebo at four weeks (–1.1, 95% confidence interval [CI], –1.4 to –0.8, $P < 0.0001$ for aboBoNTA 1,000 U; –0.9, 95% CI, –1.2 to –0.6, $P < 0.0001$ for aboBoNTA 500 U).
2. There were no studies that directly compared aboBoNTA to other BoNTA products. One indirect treatment comparison (ITC) provided by the manufacturer was reviewed by the CADTH Common Drug Review (CDR). This study compared aboBoNTA against other BoNTA products. The results of the ITC suggested that the three botulinum neurotoxins approved for treating ULS (aboBoNTA, onaBoNTA, and incoBoNTA) likely have similar treatment effects in patients with post-stroke spasticity. However, this comparison was limited by substantial heterogeneity among studies and the assumptions required to facilitate the pooling of data for analysis. These limitations precluded any definitive conclusions regarding the comparative efficacy and safety of aboBoNTA with other BoNTA drugs. Thus, there is no evidence to suggest that there is any therapeutic advantage of aboBoNTA compared with incoBoNTA and onaBoNTA.
3. AboBoNTA does not address any unmet need that is not currently met by other BoNTA products that are reimbursed for the treatment of ULS.

Of Note:

CDEC noted that aboBoNTA is the third product in the neurotoxin type A class of botulinum neurotoxins approved for treating ULS, and that all three BoNTA 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 who had previously experienced either failure or a poor response to botulinum toxin were excluded from the placebo-controlled trial (Study 145). The potential for the sequential use of aboBoNTA to increase the annual drug plan cost of treating patients with ULS, and the fact that this product does not fill a therapeutic gap in the treatment of ULS, led the committee to conclude that, in order to provide value to public drug plans, aboBoNTA should provide cost savings relative to other BoNTA products.

Discussion Points:

- Ninety per cent of patients included in the randomized, placebo-controlled trial (Study 145) entered an open-label extension trial (Study 148) designed to assess the safety of repeated aboBoNTA injections with a maximum study duration of 15 months. All patients were treated for a combined total of five injection cycles over the course of Studies 145 and 148.

Patients could receive doses ranging between 500 U and 1,500 U at the investigator's discretion. Overall, the safety and efficacy findings in the open-label extension trial were similar to those observed in the placebo-controlled trial.

- Outcomes reported as being important to patient groups such as the goal attainment, caregiver burden, and decreased need for restraints were not measured in the placebo-controlled trial (Study 145). Other outcomes such as ease of applying a splint and health-related quality of life were measured; however these outcomes were considered exploratory.
- No evidence was available to assess the use of aboBoNTA in patients with ULS due to causes other than stroke or traumatic brain injury. The cause of spasticity was stroke in 90.3% of patients and traumatic brain injury in 9.7% of patients in the placebo-controlled trial (Study 145). The clinical expert consulted for this review noted that the efficacy and safety profile of aboBoNTA in the treatment of ULS would be similar regardless of the underlying condition.

Background:

AboBoNTA has a Health Canada–approved indication for the symptomatic treatment of focal spasticity affecting the upper limbs in adults. AboBoNTA is available as a single-use sterile 300 U vial, and as a single-use sterile 500 U vial for reconstitution with 0.9% sodium chloride injection USP, for intramuscular use. The recommended dose of aboBoNTA in initial and sequential treatment sessions should be tailored to the individual 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 aboBoNTA. No more than 1 mL should generally be administered at any single injection site. Repeat aboBoNTA treatment should be administered 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 by CDEC, and received a recommendation to reimburse for reducing the subjective symptoms and objective signs of cervical dystonia (spasmodic torticollis) in adults with or without botulinum toxin treatment experience, if the following conditions are met: list in a manner similar to the public plan listings for other botulinum neurotoxin A products and with a reduction in price (Notice of CDEC Final Recommendation, July 2017).

Summary of CDEC Considerations:

CDEC considered the following information prepared by CDR: a systematic review of randomized controlled trials (RCTs) of aboBoNTA, one ITC submitted by the manufacturer, a critique of the manufacturer's pharmacoeconomic evaluation, and information submitted by patient groups regarding outcomes and issues important to patients with ULS.

Patient Input Information

Two patient groups responded to the call for patient input for this CDR review: March of Dimes Canada and the Multiple Sclerosis Society of Canada. The following is a summary of key information provided by the patient groups:

- ULS can greatly affect a patient's ability to carry out activities of daily living (e.g., caring for children or other family members, driving, self-care, socializing, mobility, living independently, and recreational activities), and living with the condition has been associated with unemployment.
- The impact of ULS on caregivers can also be considerable. The challenges identified for caregivers include: time constraints, risk of physical strain, feeling of difficulty/frustration, financial burdens, and problems finding appropriate and affordable treatments.
- Patients reported that ULS is typically managed through exercise or with muscle relaxants and anticonvulsant medications. Of those patients who indicated that they use a medication, few patients (less than 5%) were very satisfied with the treatment effect. In addition, most medications prescribed for the management of ULS carry troublesome side effects including weakness, numbness and tingling, blurred vision, fatigue, and difficulty sleeping.
- Responders from both patient groups expressed concerns about the high costs of the medications and the challenges when a specialist is required to provide the treatment, instead of a family doctor.
- Patients expect that aboBoNTA will provide an effective therapy for ULS for up to 20 weeks without the adverse effects that are commonly observed for muscle relaxant or anticonvulsant medications.

Clinical Trials

One double-blind RCT was included in the CDR systematic review. Study 145 (N=243) was a phase III placebo-controlled RCT which assessed the efficacy and safety of aboBoNTA versus placebo for the treatment of adult patients with ULS, with or without prior botulinum neurotoxin therapy. Patients were randomized to receive either aboBoNTA (500 U or 1,000 U, single intramuscular injection into clinically indicated muscles) or placebo, in a ratio of 1:1:1; 81 patients were assigned to each treatment arm.

Outcomes

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

- MAS: A commonly used, validated 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. A 1-point change in the MAS score is considered to be clinically meaningful.
- Physician's Global Assessment (PGA): A 9-point categorical scale, conducted by the investigator, to assess the treatment response. The score ranges from –4 to +4; higher score indicates better results. A minimal clinically important difference for this outcome has not been established.
- Disability Assessment Scale (DAS): A questionnaire that measures the degree of the patient's functional impairment in four domains: hygiene, dressing, limb position, and pain. In each domain the score ranges from 0 to 3. A decrease in the DAS score is considered an improvement. A minimal clinically importance difference for the DAS score was not identified from the literature search.
- Health-Related Quality of Life: This is assessed using two generic questionnaires: the Short Form-36 (SF-36) and the European Quality of Life-5 Dimensions, 5-level version (EQ-5D-5L).
- Other Tertiary Outcomes: Tardieu Scale score, active range of motion, Modified Frenchay Scale, and ease of applying a splint.
- Serious AEs (SAEs), total AEs, and withdrawals due to AEs.

The change from baseline in MAS score at week 4 for the PTMG was the primary outcome measure in Study 145.

Efficacy

MAS score for the PTMG at week 4: There were statistically significant, between-group differences in the mean change from baseline in the MAS score for the aboBoNTA 1,000 U group (–1.1, 95% CI, –1.4 to –0.8, $P < 0.0001$) and for the aboBoNTA 500 U group (–0.9, 95% CI, –1.2 to –0.6, $P < 0.0001$) compared with placebo. The differences between the aboBoNTA groups and placebo were considered to be clinically meaningful.

DAS score for the PTMG at week 4: There were no statistically significant, between-group differences in mean change from baseline in the DAS for aboBoNTA compared with placebo (–0.1, 95% CI, –0.4 to 0.1, $P = 0.26$; and –0.2, 95% CI, –0.4 to 0.0; $P = 0.08$, in the aboBoNTA 500 U and aboBoNTA 1,000 U groups, respectively).

PGA at week 4: there were statistically significant, between-group differences in mean change from baseline in PGA score for the aboBoNTA 1,000 U group (1.1, 95% CI, 0.8 to 1.4, $P < 0.0001$) and the aboBoNTA 500 U group (0.6, 95% CI, 0.3 to 1.0, $P = 0.0003$) compared with placebo.

Harms (Safety and Tolerability)

The overall AE rates were 43% in both aboBoNTA groups, and 26% in the placebo group. The most common treatment-emergent AE was nasopharyngitis (8.6%, 1.2%, and 1.2% in the aboBoNTA 500 U, aboBoNTA 1,000 U, and placebo groups, respectively). SAEs were rare (4% in each group). The number of patients who withdrew due to AEs were 1 (1.2%), 1 (1.2%), and 3 (3.7%) in the aboBoNTA 500 U, aboBoNTA 1,000 U, and placebo groups, respectively. Two deaths occurred during the study: one patient died in the aboBoNTA 500 U group, and one patient died in the placebo group. Neither of the deaths was considered to be treatment related. Notable harms including muscle weakness and injection site pain occurred in less than 5% of patients, and no patients were reported to have experienced dysphagia.

Indirect Treatment Comparison

In the absence of direct evidence comparing aboBoNTA to other active treatments, the manufacturer submitted an ITC. The objective of the analysis was to compare the relative efficacy and safety of aboBoNTA to onaBoNTA and incoBoNTA. In total, 18 trials were included, to examine the relative benefits and harms of three BoNTAs for the treatment of adult patients with ULS. The reported outcomes of interest included: the change in MAS score measured at week 4 to week 6, and at week 12; the change in DAS scores measured at week 4 to week 6, and at week 12; and the rate of AEs at week 12. A limited number of studies were available to assess some outcome measures, and several key baseline patient characteristics (treatment experience, disease severity, and background therapy) were not reported in sufficient detail to allow for a comprehensive assessment of the clinical heterogeneity between trials. Where trial characteristics were reported and heterogeneity was identified (for example, with interventions and outcome measures assessed), the potential impact of such heterogeneity on treatment effects is unknown, as it was not explored or described in sufficient detail. Results of this analysis suggest that the three botulinum toxins (aboBoNTA, onaBoNTA, and incoBoNTA) are likely to have similar treatment effects in patients with post-stroke spasticity. However, these results are limited by the small number of studies for some outcomes, the high degree of heterogeneity between studies, and the large number of assumptions required to facilitate the pooling of data for analysis.

Cost and Cost-Effectiveness

The price of aboBoNTA is $428.40 and $714.00 per 300 U and 500 U single-use vials, respectively. The recommended initial dose is individually tailored. In the pivotal trial, 500 U or 1,000 U were used intramuscularly, divided among selected muscles.

The manufacturer submitted a cost-comparison analysis using a budget impact analysis to estimate total drug costs based on claims for onaBoNTA and incoBoNTA from April 2015 to March 2016. Claims from the Ontario Drug Benefit (ODB) were obtained based on the limited use code for focal spasticity. Clinical similarity was assumed, on the basis of an unpublished ITC submitted by the manufacturer comparing aboBoNTA with onaBoNTA and incoBoNTA. Drug costs were obtained from ODB list prices and the manufacturer; partially used vials were assumed to be wasted. All other costs, such as for administration and monitoring, were assumed equal. The manufacturer considered a scenario where all claims reimbursed for the comparators (onaBoNTA and incoBoNTA) were replaced by aboBoNTA. Determination of dose per claim for aboBoNTA was in line with a 3:1 or lower ratio as observed in clinical trials for cervical dystonia, with a maximum dose of 1,500 U allowed for aboBoNTA. The manufacturer estimated that, should claims be reimbursed for aboBoNTA instead of for onaBoNTA and incoBoNTA for ULS, an estimated annual savings of approximately $116,000 would be realized (1.3%).

Key limitations in the manufacturer's analysis included: uncertainty in the assumption of clinical similarity between comparators; the use of a budget impact analysis approach assuming a 100% market share for aboBoNTA rather than a patient-centric cost analysis; inappropriate dose conversions, where the upper limit of aboBoNTA dosing was capped below equivalent doses of comparators; and an extended treatment duration scenario based on an interim analysis of an observational study which included time to re-treatment without considering dosing or clinical outcomes.

Based on CDR reanalyses, considering a 2.5:1 dosing ratio of aboBoNTA to comparators and a 12-week duration of effect:

- Based on the observed use of onaBoNTA from claims data, aboBoNTA ($5,971 per patient per year) was on average $297 more expensive than onaBoNTA ($5,674 per patient per year).
- Based on the observed use of incoBoNTA from claims data, aboBoNTA ($6,828 per patient per year) was on average $669 more expensive than incoBoNTA ($6,158 per patient per year).

The cost per unit of aboBoNTA would need to be reduced by 4.9% to be similar in cost to onaBoNTA, and reduced by 9.8% to be similar in cost to incoBoNTA. CDR considered there to be insufficient data available to estimate costs based on possible differences in duration of effect among comparators.

AboBoNTA is priced to be equivalent to the cost of onaBoNTA when a 2.5:1 dosing ratio is assumed, but is 8% more expensive than incoBoNTA at the same 2.5:1 dose-equivalent unit. The vial sizes available for aboBoNTA compared with the other BoNTA drugs also increase the potential for higher wastage, based on the dosing of aboBoNTA as compared with onaBoNTA and incoBoNTA, and thus higher costs.

CDEC Members:

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

September 20, 2017

Regrets:

None

Conflicts of Interest:

None