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CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

AbobotulinumtoxinA (Dysport Therapeutic — Ipsen Biopharmaceuticals Canada, Inc.)
Indication: To reduce the subjective symptoms and objective signs of cervical dystonia (spasmodic torticollis) in adults

RECOMMENDATION:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that abobotulinumtoxinA be reimbursed 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:

Conditions:
1. List in a manner similar to the public plan listings for other botulinum neurotoxin A products.
2. Reduction in price.

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Abbreviations

aboBoNTA	abobotulinumtoxinA (Dysport Therapeutic)
AE	adverse event
BoNT	botulinum neurotoxin
CD	cervical dystonia
CDEC	CADTH Canadian Drug Expert Committee
CDR	CADTH Common Drug Review
CI	confidence interval
DB	double-blind
HC	Health Canada
incoBoNTA	incobotulinumtoxinA (Xeomin)
ITC	indirect treatment comparison
MCID	minimal clinically important difference
onaBoNTA	onabotulinumtoxinA (Botox)
RCT	randomized controlled trial
SF-36	Short Form (36) Health Survey
ST	spasmodic torticollis
TWSTRS	Toronto Western Spasmodic Torticollis Rating Scale
VAS	visual analogue scale

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Recommendation:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that abobotulinumtoxinA (aboBoNTA, Dysport Therapeutic) be reimbursed for reducing the subjective symptoms and objective signs of cervical dystonia (CD) (spasmodic torticollis [ST]) in adults with or without botulinum toxin treatment experience if the following conditions are met:

Conditions:

1. List in a manner similar to the public plan listings for other botulinum neurotoxin A products.
2. Reduction in price.

Reasons for the Recommendation:

1. Two randomized, placebo-controlled trials demonstrated statistically significant improvements in the primary outcome (Toronto Western Spasmodic Torticollis Rating Score [TWSTRS] score) with a single dose of aboBoNTA as compared with placebo at four weeks (between-group mean difference [MD] of –6.0 points; 95% CI, –10.6 to –1, $P = 0.013$ in Study 45; and MD of –8.9 points; 95% CI, –12.94 to –4.74, $P < 0.0001$ in Study 51). The improvement in TWSTRS total score observed for aboBoNTA at week 4 was maintained at week 8 and, to a lesser extent, at week 12 in both studies.
2. At the submitted price, the cost of aboBoNTA exceeds the cost of both onabotulinumtoxinA (onaBoNTA, Botox) and incobotulinumtoxinA (incoBoNTA, Xeomin).

Of Note:

No evidence was available to evaluate whether sequential use of aboBoNTA would be effective in individuals who have had a previous poor response to botulinum toxin. Patients with poor response to botulinum toxin were excluded from the trials.

Discussion Points:

- CDEC noted that there are currently no data to suggest clinical superiority of aboBoNTA in comparison with the two other botulinum toxin A drugs available in Canada. In addition to the two placebo-controlled trials, CDEC considered four onaBoNTA-controlled randomized controlled trials (RCTs) using dosing outside of that approved by Health Canada (HC) for aboBoNTA. In these trials, aboBoNTA (in a dose ratio of aboBoNTA versus onaBoNTA ranging from 1.7:1 to 4:1) had a similar safety and uncertain comparable efficacy profile versus onaBoNTA in the treatment of patients with CD who had a stable response to onaBoNTA previously. A network meta-analysis by Han and an indirect treatment comparison (ITC) submitted by the manufacturer found that the efficacy and safety profile of aboBoNTA, onaBoNTA, and incoBoNTA appeared similar four weeks after injection.
- CDEC also noted that no direct evidence assessed the duration of effect with the aboBoNTA treatment compared with onaBoNTA and incobotulinumtoxinA in the treatment of CD.

Background:

AboBoNTA has an HC indication to reduce the subjective symptoms and objective signs of CD (ST) in adults. AboBoNTA is a type A botulinum neurotoxin (BoNT) (neuromuscular blocking agent) purified from *Clostridium botulinum*. It is available as a sterile

lyophilized powder for solution for injection (300 U and 500 U per vial). The HC–approved dose is initially 500 U given intramuscularly as a divided dose among affected muscles in patients with or without a history of prior treatment with botulinum toxin. Re-treatment doses in clinical trials were within the range of 250 U to 1,000 U. Re-treatment, if needed, should not occur in intervals of less than 12 weeks. Doses exceeding 1,000 U are not recommended.

Summary of CDEC Considerations:

The Committee considered the following information prepared by CADTH Common Drug Review: a systematic review of RCTs and pivotal studies of aboBoNTA in the treatment of adult patients (18 years or older) with CD (ST); a critique of the manufacturer's pharmacoeconomic evaluation; and patient group-submitted information about outcomes and issues important to patients with CD.

Patient Input Information

One patient group, the Dystonia Medical Research Foundation Canada (DMRFC), submitted input for this review. The information provided by DMRFC was obtained from an online patient survey and two interviews.

Symptoms of CD:

- Patients with CD experience a range of symptoms that cause physical and emotional distress. Physically, patients highlight neck pain as an important symptom to control. Other symptoms include fatigue, involuntary muscle action that causes twisting of the torso, shaking, and twisting of the head, general tremors, and physical activity limitations. Many patients are no longer able to work and cannot enjoy or participate in leisure and social events. The pain, isolation, and physical limitations erode patients' autonomy, confidence, and sense of well-being, putting them at risk of depression and anxiety.

Current treatment and unmet needs:

- The great majority of the patients who responded to the survey (85%) had tried botulinum toxin A in the form of onaBoNTA, (Botox). While a majority of respondents (62%) were still using it, 13% were using incobotulinumtoxinA (incoBoNTA, Xeomin). Just over two-thirds had tried some unspecified oral treatment. Patients had also used a variety of non-drug options, including physiotherapy, acupuncture, medical marijuana, etc. This may indicate a widespread dissatisfaction with the efficacy of any one therapy and a great desire to find something or some combination that works. Only a handful of patients (four out of 80) reported that their current treatment provided "excellent" control of their headaches; another six out of 80 responders reported headache control as "very good." With respect to neck pain, which was described as the most important symptom that patients would like to control, just under one-quarter thought the current treatment provided "excellent" or "very good" control. Two adverse events (AEs) were reported frequently by the responders: "muscle weakness near injection area" and "headaches, muscle stiffness, neck, or back pain." Financial difficulty in obtaining therapy, trouble finding a specialist with expertise in treating CD, and the need to travel long distances to receive treatment were also potential barriers for some patients.

Experience with aboBoNTA:

- One patient who had used the drug said that it improved his or her symptoms. The caregiver of a patient who had used it said the patient was able to have less frequent injections compared with onaBoNTA.

Clinical Trials

The systematic review included two pivotal, placebo-controlled, double-blind (DB) RCTs (Study 45 and Study 51) that compared aboBoNTA (500 U, single intramuscular injection) with placebo in patients with CD. Patients with CD, with or without the previous experience of onaBoNTA treatment, were included in the two trials. A total of 196 patients were randomized, including 80 and 116 patients in Study 45 and Study 51, respectively. In Study 45, the discontinuation rates at week 12 were [redacted] and [redacted] in the aboBoNTA group and placebo group, respectively. In Study 51, the discontinuation rates at week 12 were [redacted] and [redacted] in the aboBoNTA group and placebo group, respectively.

Outcomes

Outcomes were defined a priori in the CADTH Common Drug Review (CDR) systematic review protocol. Of these, the Committee discussed the following:

TWSTRS total score and TWSTRS subscale scores (severity, disability, and pain): TWSTRS was developed specifically for clinical trials in CD and is accepted by the FDA and HC. It measures three domains in three subscales: symptom severity (11 items, clinician-rated); disability (six items, patient-rated); and pain (three items, patient-rated). The TWSTRS severity (range: 0 to 35), disability (range: 0 to 30), and pain (range: 0 to 20) subscales assess distinct aspects of CD. The TWSTRS total score (range: 0 to 85) reflects the sum of the three subscale scores: the higher the score, the more severe the CD condition. A decrease in TWSTRS total or subscale score indicates an improvement in the patient's CD. No minimal clinically important difference (MCID) was identified.

Patient and investigator's visual analogue scale (VAS) symptom assessments: The patient and investigator assessment of change in the signs and symptoms of CD was assessed using a VAS, with the centre being no change from baseline. The VAS ranges from 0 to 100 mm, where 0 mm indicates much worse and 100 mm indicates symptom-free.

Pain (VAS scores for pain): VAS is a common approach to use in measuring pain. The score ranges from 0 mm to 100 mm. There is evidence of validity for the use of VAS for muscle pain measurement. However, no information was identified that directly assesses the validity or MCID for VAS in CD.

SF-36 Health Survey: The Short Form (36) Health Survey (SF-36) is a questionnaire that assesses health-related quality of life. The SF-36 includes eight individual domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, mental health, and role emotional. The eight individual domains can be further aggregated into a physical component summary (SF-36 PCS) and a mental component summary (SF-36 MCS). Each scale ranges from 0 (worst health possible) to 100 (best health possible). The use of the SF-36 has been assessed in patients suffering from CD and has been found valid and reliable. No MCID was identified for CD, although the generally recommended MCID is 2 points for the SF-36 PCS and 3 points for SF-36 MCS.

Treatment response: Treatment response was defined as being evident in those patients who had a decrease in TWSTRS total score of at least 30%, and at least 10 points, compared with baseline.

Treatment success and investigator's global assessment — efficacy and safety for CD: As reported by the manufacturer, this measure is an investigator-reported global impression of change. Investigators report their assessment of patients as either positive change, or harmful change. Treatment success was defined as patients with a global efficacy assessment of "Better" or "Much better" and a safety assessment of no worse than "Moderate." No additional information was found in the literature that provided evidence of the validity or reliability of such a measure.

Duration of effect: The duration of effect or duration of response (time to re-treatment) was defined as the time between the date of administration of the study medication and the date of the need for re-treatment. It was only calculated for patients who responded. Re-treatment is indicated if the response to treatment on the TWSTRS total score returns to a decrease from baseline of less than 10%.

Harms (Serious Adverse Events, Total Adverse Events, and Withdrawals Due to Adverse Events)

The primary outcome assessed in the two RCTs was TWSTRS total score at week 4. Outcomes that indicated a reduction in symptoms (e.g., TWSTRS total score, TWSTRS subscales, patient and investigator VAS symptom assessments, pain, disability, and quality of life) were considered the important outcomes by the patient group.

Efficacy

In Study 45, the adjusted mean change from baseline (mean ± standard error [SE]) of the TWSTRS total score at week 4 was 9.6 ± 2.0 points in the aboBoNTA group, compared with 3.7 ± 1.8 points in the placebo group. The between-group MD of changes from baseline (aboBoNTA minus placebo) was statistically significant (–6.0 points; 95% CI, –10.6 to –1, $P = 0.013$). In Study 51, the adjusted least squares mean ± SE of change from baseline in TWSTRS total score at week 4 was 15.58 ± 1.95 in the aboBoNTA

group, compared with 6.74 ± 2.03 in the placebo group (95% CI, –12.94 to –4.74, *P* < 0.0001). The improvement in TWSTRS total score observed for aboBoNTA at week 4 was maintained at week 8 and, to a lesser extent, at week 12 in both studies. Subgroup analysis data for TWSTRS total score in Study 51 found that the results for TWSTRS total score at weeks 4, 8, and 12 demonstrated similar efficacies between BoNT-naive and BoNT-experienced patients.

In both Study 45 and Study 51, TWSTRS subscales (severity, disability, and pain) demonstrated greater improvement in the aboBoNTA group compared with the placebo group from week 4 to week 12. In Study 45, the between-group differences of change from baseline at weeks 4, 8, and 12 in three TWSTRS subscales were all statistically significant in favour of aboBoNTA treatment. However, in Study 51, no statistical analysis was performed to assess the treatment group differences for the TWSTRS subscales (severity, disability, and pain).

In Study 45, the statistically significant improvement observed in the aboBoNTA group at week 4 was maintained at week 8 and week 12; patients were more symptom-free in the aboBoNTA group compared with patients in the placebo group at both week 8 and week 12. By week 12, ratings of the signs and symptoms had nearly returned to baseline in the aboBoNTA group, but remained significantly worse than baseline in the placebo group.

In both Study 45 and Study 51, VAS scores for pain showed greater improvement in the aboBoNTA group compared with the placebo group from week 4 to week 12. However, the statistically significant, between-group differences in changes from baseline were reported in Study 45 at week 4 and week 8, but not at week 12. By week 12, the VAS pain score had nearly returned to baseline in both treatment groups.

In Study 51, it was reported that the change from baseline for SF-36 scores was not statistically significant in either of the treatment groups.

In Study 45, the proportion of responders in the aboBoNTA group was higher than in the placebo group (aboBoNTA versus placebo) at week 4 (38% versus 16%), week 8 (27% versus 9%), and week 12 (19% versus 7%). In Study 51, the proportion of responders was higher in the aboBoNTA group than in the placebo group at week 4, week 8, and week 12. In both RCTs, there were statistically significantly more responders among patients who took aboBoNTA compared with patients who took placebo at week 4 and week 8, but not at week 12.

Treatment Success/Investigator's Global Assessment (Efficacy and Safety)

In Study 45, numerically more patients in the aboBoNTA group (35%) than patients in the placebo group (23%) were considered treatment successes at week 12. There was no statistically significant difference between aboBoNTA and placebo in treatment success. These results should be interpreted with caution due to the very high discontinuation rate in the DB phase. In Study 51, treatment success rates were 58% and 16% in the aboBoNTA group and placebo group, respectively.

In the DB phase of Study 45, it was reported that for the patients who responded to aboBoNTA, the duration of the effect (mean ± SD) was 22.8 ± 12.5 weeks (range, 9 weeks to 46 weeks). In the open-label extension phase of Study 45, the mean durations of effect in the reported three retreatments were [redacted], [redacted], and [redacted], respectively. The range of the duration of effect was from [redacted]. In the open-label extension phase of Study 51, the mean durations of effect (± SD) were [redacted], [redacted], and [redacted], respectively, in the three treatment cycles ([redacted]). The overall range of the duration of the effect was [redacted].

Overall, efficacy results from Study 45 and Study 51 indicated a treatment effect and were consistent across primary and most of the secondary outcomes, demonstrating that aboBoNTA is more effective than placebo for reducing the symptoms and signs of CD. However, due to several methodological limitations of the RCTs, especially the high dropout rate in the DB phase in Study 45, the findings reported in Study 45 after week 4 should be interpreted with caution.

In addition to the two pivotal, placebo-controlled RCTs, four onaBoNTA-controlled RCTs using dosing outside of HC–approved doses for aboBoNTA reported that aboBoNTA (in a dose ratio of 1.7:1 to 4:1 for aboBoNTA versus onaBoNTA) had similar safety and uncertain comparable efficacy versus onaBoNTA in the treatment of patients with CD who had a stable response to onaBoNTA previously. No direct evidence assessed the duration of effect with the aboBoNTA treatment compared with onaBoNTA and

incoBoNTA in the treatment of CD. A network meta-analysis by Han and an ITC submitted by the manufacturer found that the efficacy and safety profiles of aboBoNTA, onaBoNTA, and incoBoNTA appeared similar at week 4 after injection.

Harms (Safety and Tolerability)

In general, the safety profile for aboBoNTA was similar to that for placebo. Study 45 showed a numerically higher incidence in aboBoNTA groups (5% greater than placebo) for injection site pain (38% versus 23%), neck/shoulder pain (38% versus 30%), and tiredness (35% vs. 30%), all of which were higher than in the placebo groups in both RCTs. The overall incidence of AEs reported in Study 51 was much lower than in Study 45, which may be due to the differences in AE reporting between the two studies. That is, in Study 45, the AEs were assessed according to a checklist of 10 AEs considered to be associated with botulinum toxin therapy of neck muscles (dysphagia, dry mouth, voice changes, neck muscle weakness, jaw weakness, limb weakness, tiredness, respiratory difficulties, discomfort at injection site, and visual difficulties). In Study 51, a checklist was not described. Serious AEs were rarely reported in both studies. During the DB phase, no patients withdrew due to AEs. No patients died in either of the studies.

Cost and Cost-Effectiveness

The price of aboBoNTA is $428.40 and $714.00 per 300 U and 500 U single-use vial, respectively. The recommended initial dose is 500 U intramuscularly as a divided dose among affected muscles in patients with and without a prior history of treatment with botulinum toxin, with re-treatment of 250 U to 1,000 U divided among affected muscles when the effect of a previous injection has diminished, but no sooner than 12 weeks after the previous injection. The recommended initial dose of aboBoNTA is $714, and from $428 to $1,428 per patient for retreatments.

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 CD. Clinical similarity was assumed on the basis of four head-to-head trials comparing initial doses of aboBoNTA with onaBoNTA, as well as an unpublished ITC adding incoBoNTA as a comparator. 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, with a maximum dose of 1,000 U allowed for aboBoNTA.

The manufacturer estimated that, should claims be reimbursed for aboBoNTA instead of for onaBoNTA and incoBoNTA for CD, an estimated annual savings of approximately $174,000 would be realized.

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 resulting in only the lowest doses of aboBoNTA having a duration beyond 12 weeks relative to comparators.

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 ($4,641 per patient per year) was on average $189 more expensive than onaBoNTA ($4,452 per patient per year).
- Based on the observed use of incoBoNTA from claims data, aboBoNTA ($4,492 per patient per year) was on average $502 more expensive than incoBoNTA ($3,990 per patient per year).

A CDR reanalysis considering only dose distributions used in head-to-head clinical trials comparing aboBoNTA and onaBoNTA yielded similar results to the CDR reanalysis based on claims data.

Based on CDR reanalyses, the cost per unit of aboBoNTA would need to be reduced by 3.3% to be cost-neutral to onaBoNTA, and reduced by 11.2% to be cost-neutral to incoBoNTA.

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-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, and Dr. Harindra Wijeysundera.

June 21, 2017 Meeting:

Regrets:

Two CDEC members did not attend the meeting.

Conflicts of Interest:

None