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CADTH Reimbursement Recommendation

IncobotulinumtoxinA (Xeomin)

Indication: For the treatment of chronic sialorrhea associated with neurological disorders in adults

Sponsor: Merz Pharmaceuticals GMBH

Final recommendation: Reimburse with conditions

CADTH

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Xeomin?

CADTH recommends that Xeomin should be reimbursed by public drug plans for the treatment of chronic sialorrhea associated with neurological disorders if certain conditions are met.

Which Patients Are Eligible for Coverage?

Xeomin should only be covered to treat adult patients with moderate to severe chronic troublesome sialorrhea who do not have swallowing difficulties.

What Are the Conditions for Reimbursement?

Xeomin should only be reimbursed if prescribed by a specialist with experience in managing neurological conditions, and the cost of Xeomin is reduced.

Why Did CADTH Make This Recommendation?

- Evidence from 1 clinical trial demonstrated that Xeomin was better than placebo in reducing the salivary flow rate.
- Xeomin may address some of the needs that are important to patients, including managing the frequency and severity of sialorrhea.
- Based on public list prices, Xeomin in combination with standard of care (i.e., non-pharmacological strategies for managing sialorrhea) is not considered cost-effective at a willingness-to-pay (WTP) threshold of $50,000 per quality-adjusted life-year (QALY). Economic evidence suggests that a price reduction of at least 30% is needed to ensure Xeomin is cost-effective at that WTP threshold.
- Based on public list prices, the 3-year budget impact is expected to be at least $31 million. The committee discussed the potential that the budget impact for Xeomin could be much higher than estimated.

Additional Information

What Is Chronic Sialorrhea?

Sialorrhea, or drooling, can occur when there is excessive saliva production or when saliva pools in the mouth because of swallowing and/or neuromuscular dysfunction. Sialorrhea is associated with several neurological conditions in adults, including Parkinson's disease, atypical parkinsonism, stroke, traumatic brain injury, amyotrophic lateral sclerosis, multiple sclerosis, cerebral palsy, and dementias including Alzheimer disease. Chronic troublesome sialorrhea can lead to speech difficulties, facial skin maceration, bad breath, and infections. It is not known how many people in Canada suffer from chronic troublesome sialorrhea.

Unmet Needs in Chronic Sialorrhea

Most of the medications used to treat chronic sialorrhea are associated with numerous adverse effects that patients with chronic sialorrhea find difficult to tolerate. Despite several available medications, there remains a need for a treatment that effectively reduces the frequency and severity of sialorrhea and with minimal adverse effects.

How Much Does Xeomin Cost?

Treatment with Xeomin is expected to cost approximately $1,073 per patient per year assuming 3.25 administrations per year.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that incobotulinumtoxinA should be reimbursed for the treatment of chronic sialorrhea associated with neurologic disorders in adults only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One randomized, double-blind, placebo-controlled study (SIAXI, N = 184) in adults with moderate to severe sialorrhea resulting from neurologic conditions demonstrated that 4 weeks after a single injection, incobotulinumtoxinA 100 U was superior to placebo in terms of reducing the salivary flow rate and patient reported impression of change. This was based on LS-Mean differences in unstimulated salivary flow rate (uSFR) and the patient reported global impression of change scale (GICS) of −0.09 g/min (95% confidence interval [CI], −0.15 to −0.03; P = 0.004) and 0.58 (95% CI, 0.22 to 0.94; P = 0.002), respectively. Treatment effects in the uSFR and GICS were also observed at weeks 8 and 12 post-injection. Treatment with incobotulinumtoxinA was tolerated in most patients, and adverse effects were generally manageable, with some infrequent but expected notable harms related to toxin spread (e.g., dry mouth, dysphagia). Patients identified the need for a treatment that manages the frequency and severity of sialorrhea with mild or rare adverse effects; results of the SIAXI study demonstrate that incobotulinumtoxinA may address these needs. The SIAXI study was too short in duration to determine long-term adverse effects.

Using the sponsor submitted price for incobotulinumtoxinA and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for incobotulinumtoxinA in combination with standard of care (SoC) was $67,239 per quality-adjusted life-year (QALY) compared with SoC. At this ICER, incobotulinumtoxinA is not cost-effective at a $50,000 per QALY willingness-to-pay (WTP) threshold for adult patients with neurologic disorders who have chronic sialorrhea. A reduction in price of at least 30% is required for incobotulinumtoxinA to be considered cost-effective at a $50,000 per QALY threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason
Initiation	
1. Adult patients with moderate to severe chronic troublesome sialorrhea, defined as: 1.1. Sialorrhea lasting for ≥ 3 months 1.2. DSFS sum score ≥ 6 and DSFS scores for both severity and frequency ≥ 2 at the time of initial request for reimbursement.	In the SIAXI study, incobotulinumtoxinA reduced salivary flow rate in adults with chronic troublesome sialorrhea, which was defined as sialorrhea lasting for ≥ 3 months with DSFS sum score ≥ 6, DSFS scores for both severity and frequency ≥ 2, and mROMP Section 3 Drooling, Item A score ≥ 3 at both screening and baseline.
2. Patients must not have evidence of dysphagia.	Absence of clinically relevant dysphagia was an inclusion criterion for the main and extension phases of the SIAXI study.

Reimbursement condition	Reason
3. The maximum duration of initial authorization is 16 weeks.	The dosage regimen recommended by Health Canada for incobotulinumtoxinA is a total dose of 100 U no sooner than every 16 weeks. In the SIAXI study, patients demonstrated a response to treatment as early as 4 weeks after receiving the initial injection.
Renewal	
4. Patients must have exhibited, based on the opinion of the treating physician in discussion with the patient and/or caregiver, a reduction in the severity and/or frequency of sialorrhea at the time of first renewal compared with baseline.	The clinical expert noted that response is based on clinical assessment at each visit.
5. Subsequent authorizations following the initial authorization are for a 1-year period.	In the SIAXI study, the mean changes from baseline observed in the incobotulinumtoxinA treatment group during the extension period were consistent with those observed during the main period phase for most outcomes.
Discontinuation	
6. Subsequent reimbursement must be discontinued if the treatment effect compared to the previous cycle is not maintained.	There is no evidence to demonstrate that patients would respond to subsequent cycles of treatment with incobotulinumtoxinA if the response to the previous cycle of treatment with incobotulinumtoxinA was not maintained.
Prescribing	
7. The patient must be under the care of a specialist with experience in managing neurologic conditions	Accurate diagnosis and follow-up of patients with chronic sialorrhea associated with neurologic disorders are important to ensure that incobotulinumtoxinA is prescribed to appropriate patients.
Pricing	
8. A reduction in price	The ICER for incobotulinumtoxinA in combination with SoC is $67,239 when compared with SoC. A price reduction of 30% would be required for incobotulinumtoxinA to be able to achieve an ICER of $50,000 per QALY compared to SoC.

DSFS = drooling severity and frequency scales; mROMP = modified Radboud oral motor inventory for Parkinson disease.

Implementation Guidance

1. Patients should not be required to utilize other therapies before incobotulinumtoxinA, as other available therapies used to control sialorrhea may not be appropriate for patients with various neurologic conditions.
2. Given that the underlying mechanism of sialorrhea is similar across various neurologic conditions, patients with moderate to severe chronic troublesome sialorrhea should be eligible for reimbursement of incobotulinumtoxinA regardless of their neurologic disorder.
3. As per Health Canada–approved dosage, the maximum dose of incobotulinumtoxinA should not exceed 100 U and should be administered at least 16 weeks apart.

4. CDEC noted that some jurisdictions may require longer or shorter duration for subsequent authorizations following the initial authorization than the recommended 1-year period.
5. IncobotulinumtoxinA should only be administered by physicians with the appropriate qualifications and experience in the therapeutic use of incobotulinumtoxinA for chronic sialorrhea. The physician administering incobotulinumtoxinA may or may not be the prescribing specialist.

Discussion Points

- CDEC discussed that there is considerable uncertainty associated with the results of the SIAXI study due to limited confidence in the outcome measures used (uSFR, GICS, drooling severity and frequency scales [DSFS], or modified Radboud oral motor inventory for Parkinson disease [mROMP]), which were not validated and had no estimated minimal important differences (MIDs). CDEC noted that these outcomes are not routinely used in clinical practice and are subjective apart from uSFR, which is an impractical outcome in a real-world setting. Thus, post-incobotulinumtoxinA treatment changes in sialorrhea had unclear clinical significance and relevance to the health-related quality of life (HRQoL) of patients. CDEC acknowledged the lack of validated outcome measures for clinical studies of sialorrhea as well as an international consensus statement recommending salivary flow measurements and the DSFS (the latter being an exploratory outcome in SIAXI). In addition, the clinical experts noted that in clinical practice, treatment response is usually assessed subjectively in a similar manner to some outcome measures assessed in the SIAXI study and that the between-group differences reported in the SIAXI study were clinically meaningful.
- CDEC noted challenges in identifying patients most appropriate for therapy (those with moderate to severe chronic troublesome sialorrhea) and highlighted the lack of evidence regarding potential differences in treatment effect depending on sialorrhea severity and neurologic conditions. However, the clinical expert noted to CDEC that specialists with experience in managing neurologic conditions are able to identify patients appropriate for therapy with incobotulinumtoxinA.
- CDEC discussed the challenges in identifying discontinuation criteria. The clinical expert noted to CDEC that treatment should be discontinued when it is not efficacious or when adverse events (AEs) develop, such as swallowing or dental problems. These decisions should be made by patients in consultation with the treating specialist.
- In the SIAXI study, patients were eligible to enrol in the extension period of dose-blinded active treatment if there was continued absence of clinically relevant dysphagia defined as mROMP score for Section 2 Swallowing Symptoms, Item A ≤ 2 and Item C ≤ 3. CDEC discussed that treatment should be discontinued in patients who experience dysphagia.
- CDEC discussed that there is no comparative evidence on the efficacy of different botulinum neurotoxins (BoNTs) for the treatment of chronic sialorrhea associated with neurologic disorders and the lack of evidence in patients with a variety of neurologic conditions.
- CDEC discussed the potential budget impact of incobotulinumtoxinA. The size of the population who may receive incobotulinumtoxinA in practice was considered uncertain. The sponsor estimated the budget impact of incobotulinumtoxinA would be approximately $4.8 million over 3 years, while the CADTH base case estimate was approximately

$31.5 million over 3 years. If alternate assumptions were used to assess the proportion of patients with neurologic conditions eligible for incobotulinumtoxinA, the budget impact could be as high as $143.1 million over 3 years.

Background

IncobotulinumtoxinA has a Health Canada indication for the treatment of chronic sialorrhea associated with neurologic disorders in adults. IncobotulinumtoxinA is a purified botulinum neurotoxin type A (BoNT-A) free from complexing proteins that is produced from anaerobic fermentation of *Clostridium botulinum* Hall strain. incobotulinumtoxinA is available as powder for solution for injection 50 and 100 units per vial. the dosage regimen recommended by Health Canada is a total dose of 100 U (30 U per side in the parotid glands and 20 U per side in the submandibular glands) every 16 weeks. The timing for repeat treatment should be determined based on the clinical needs of the individual patient, and no sooner than every 16 weeks.

Sources of Information Used by the Committee

To make their recommendation, the committee considered the following information:

- a review of 1 phase III randomized controlled trial in adult patients with moderate to severe sialorrhea resulting from neurologic conditions
- patients' perspectives gathered by Parkinson Québec patient group
- input from public drug plans that participate in the CADTH review process
- a clinical specialist with expertise diagnosing and treating patients with chronic sialorrhea
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Input was provided by 1 patient group, Parkinson Québec, for this review. Parkinson Québec is a not-for-profit organization that supports patients with Parkinson disease in Québec through advocacy, service development, research funding, revenue development, communication, and network management. Parkinson Québec distributed an online survey to traditional users of their services (individuals living with PD and their caregivers). The survey was promoted through their newsletter and social networks between 19 January 2021 and 1 March 2021. Respondents had to be individuals living with PD and sialorrhea or their caregivers, at least 18 years of age, and Québec residents. Among the respondents, 138 individuals living with PD (47%) and 44 caregivers (40%) reported sialorrhea; of these, 116 individuals living with PD and 36 caregivers fully completed the survey.

Respondents were asked how sialorrhea impacted their lives. Approximately one-third of individuals with PD reported that sialorrhea impacted various aspects of their day-to-day lives including their self-esteem, social discomfort, eating/swallowing, and speaking/communicating. Approximately 40% to 50% of caregivers reported that sialorrhea impacted their loved ones' self-esteem, social discomfort, personal relationships, speaking/communicating, and eating/swallowing. The most common methods used by individuals living with PD to manage sialorrhea were tissues or cloths to wipe drool (87%), followed by chewing gum (17%) and muscle exercises (16%). Few individuals living with PD had used medications (5%) or BoNTs (1%) to manage sialorrhea. Respondents were asked to indicate their perceptions regarding the effectiveness of methods currently used to manage sialorrhea. Overall, 61% to 63% of individuals living with PD and 40% to 47% of caregivers were satisfied with the management of their sialorrhea. Approximately one-third of individuals with PD and 43% of caregivers agreed that there was a need for new treatments to manage sialorrhea. Respondents were asked to indicate their expectations for new treatments for sialorrhea. Overall, 82% of individuals with PD and 77% of caregivers desired government coverage of treatments, while 65% of individuals with PD and 71% of caregivers desired treatments whose side effects were rare and mild. Other desired characteristics were treatments that reduced the frequency and severity of sialorrhea, oral treatment options, and treatments with longer durations of action.

None of the survey respondents had any previous experience with incobotulinumtoxinA and only 1 respondent had received BoNT injections. No specific treatment outcomes or measures for reduced sialorrhea were identified in the patient input.

Clinician Input

Input From Clinical Experts Consulted by CADTH

One clinical specialist with expertise in the diagnosis and management of chronic troublesome sialorrhea associated with neurologic disorders in adults provided input for this review. The clinical expert stated that there is significant unmet therapeutic need for adult patients with sialorrhea. By contrast to pharmacological or surgical interventions, BoNT injections are easy to administer, have limited side effects, and are helpful for symptomatic therapy. However, they are not covered by drug plans (except in Alberta) and special access must be requested through pharma support programs that have limited resources.

IncobotulinumtoxinA would not modify the disease process, but has several advantages compared to other options. This treatment is already part of the current treatment paradigm but cannot be accessed by many patients due to funding limitations. Patients best suited for treatment with incobotulinumtoxinA would be those with significant disabling sialorrhea (e.g., those who need to use a cloth to wipe drool and those for whom the condition is socially isolating). Patients would need to attend injections every 3 to 6 months and have no major swallowing difficulties due to risk of worsening. Patients with sialorrhea that is too mild or patients with swallowing difficulties would be the least suitable for treatment with incobotulinumtoxinA. Many patients with neurologic disorders have high risks of urinary retention and confusion, and anticholinergics would not be appropriate for many of these patients.

The objective measures used in trials to assess sialorrhea (e.g., radioisotope scanning, collection cups, counting napkins) are impractical and not used in clinical practice. Response is usually assessed by taking a history. If necessary, a visual analogue scale (VAS), or tools

like the drooling severity and frequency scales (DSFS), can be used to assess response. A clinically meaningful response would be an improvement in the patient's HRQoL relating to the issues noted above. Response can be assessed subjectively at each visit as this is an injectable treatment. Treatment should be discontinued when it is not efficacious or when patients develop AEs such as swallowing problems or dental issues. IncobotulinumtoxinA should be administered in a hospital outpatient or community setting. Neurologists or physiatrists would typically be the specialists involved in the care of patients with neurologic conditions and would perform the injections.

Drug Program Input

Drug programs identified several key issues related to implementation. First, drug programs inquired whether coverage would be restricted to the specific neurologic conditions assessed in the pivotal phase III trial of incobotulinumtoxinA. The clinical expert consulted by CADTH for this review answered that the study enrolled primarily patients with PD for feasibility reasons but that the results were most likely generalizable to patients with sialorrhea arising from other neurologic conditions who may also benefit from treatment. Second, drug plans inquired regarding which criteria would be used to assess severity of sialorrhea necessitating treatment. The clinical expert noted that eligibility would be based on patient needs and clinician decision; even patients with moderate but daily issues with drooling may benefit from treatment. Third, drug plans asked whether patients should try off-label systemic medications such as anticholinergics before treatment with incobotulinumtoxinA. The clinical expert stated that these medications are not used very much in clinical practice, primary due to risks of side effects, but that disease-specific therapy would be routinely optimized in clinical practice before starting treatment with BoNTs. Fourth, drug plans asked whether combination use of incobotulinumtoxinA with anticholinergics would be excluded from coverage. The clinical expert stated that stable concomitant therapies such as anticholinergics have different mechanisms and there could be a combined benefit. Fifth, drug plans asked whether coverage would be considered for doses other than those studied in the pivotal phase III trial and the Health Canada–approved dose of 100 U. The clinical expert stated that most clinicians would use a dose close to 100 U to avoid side effects. Sixth, drug plans asked whether specific assessment scales such as DSFS or the GICS would be used to determine whether treatment should be continued. The clinical expert responded that questions similar to those used in these scales are routinely asked in clinical practice and that treatment decisions would be grounded in assessment of response by both the patient and clinician. Finally, drug plans had questions related to re-initiation of treatment following discontinuation. The clinical expert stated that treatment could be restarted and used as necessary to manage symptoms; even if treatment was discontinued due to lack of efficacy, sialorrhea may subsequently become more severe or more frequent and patients may benefit from re-treatment at a later stage. The only exception would be for patients who experienced severe side effects of incobotulinumtoxinA treatment such as swallowing impairment; in these patients treatment might not be resumed if the risk was judged as too high by the clinician.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

One phase III, double-blind (DB), placebo-controlled, multi-centre study (SIAXI) with an extension period (EP) of dose-blinded active treatment was included. The study enrolled adults aged 18 to 80 years with moderate to severe sialorrhea resulting from neurologic conditions (PD/AP, stroke, or traumatic brain injury [TBI]; N = 184). Chronic troublesome sialorrhea was defined as sialorrhea lasting for greater than or equal to 3 months with DSFS sum score of greater than or equal to 6, DSFS scores for both severity and frequency greater than or equal to 2, and modified Radboud oral motor inventory for Parkinson disease (mROMP) Section 3 Drooling, Item A score of greater than or equal to 3 at both screening and baseline. The objective of the study was to investigate the efficacy and safety of injection of 2 doses of incobotulinumtoxinA (75 U or 100 U) into the salivary glands, compared with placebo, in reducing the uSFR as well as the frequency and severity of chronic troublesome sialorrhea as evaluated by patients, caregivers and investigators using multiple rating tools (GICS, DSFS, mROMP drooling scores, and HRQoL evaluated using a VAS). The study comprised 4 consecutive 16-week treatment cycles. Following each incobotulinumtoxinA injection, patients were assessed over the course of each cycle through in-person visits to study sites and telephone calls. In the main period (MP) of the study (cycle 1), patients were randomized 2:2:1 to receive 75 U incobotulinumtoxinA, 100 U incobotulinumtoxinA, or placebo (saline) via 4 bilateral injections in the parotid and submandibular glands. For cycles 2 to 4 (EP), patients who received placebo were re-randomized 1:1 to receive either 75 U or 100 U incobotulinumtoxinA. All participants were blinded to dose level. The total duration of the study was 64 weeks. Efficacy outcomes for the 75 U incobotulinumtoxinA dose are not presented in this report because these data are not aligned with the Health Canada–approved dose (100 U).

The co-primary efficacy outcomes in SIAXI were change in uSFR from baseline to week 4 and patient reported GICS at week 4 of the MP. The secondary outcomes were change in uSFR from baseline to weeks 8 and 12 and patient reported GICS at weeks 1, 2, 8, and 12 of the MP. Exploratory outcomes included DSFS sum and subscores, mROMP speech and drooling scores, and HRQoL assessed using the EuroQol-5 Dimension-3 Level questionnaire (EQ-5D-3L) during the MP and the EP.

The mean age of the study population at the MP baseline was 65.2 years (standard deviation [SD] 11.4 years). Patients were mostly men (70.7%), White (99.5%), and predominantly had sialorrhea secondary to PD (70.7%) or stroke (19.0%). A smaller number of patients had AP (8.7%) or TBI (2.7%). The mean duration of sialorrhea was 32.7 months (SD: 34.5 months). Patients had moderate to severe sialorrhea based on DSFS and mROMP scores. Baseline demographic and clinical characteristics (including baseline uSFR, DSFS sum scores, DSFS severity scores, DSFS frequency scores, and mROMP drooling scores) were generally well balanced between study arms in the MP, as well as between the MP and EP. However, 13.9% of placebo treated patients compared to 24.3% of incobotulinumtoxinA 100 U treated patients reported prior and concomitant deep brain stimulation (DBS). The clinical expert consulted by CADTH for this review stated that this imbalance was unlikely to impact the internal validity of the study, as patients were kept on the same therapy (medications and/or DBS) before and throughout the study.

Efficacy Results

In the co-primary efficacy analysis, change in uSFR from baseline and patient reported GICS were assessed at week 4 post-injection using mixed model repeated measures. In exploratory efficacy analyses, DSFS, mROMP and HRQoL were also assessed at multiple time points post-injection including at week 4.

At week 4 of the MP, the least square (LS)-Mean change in uSFR (SE; 95% CI) in the incobotulinumtoxinA 100 U arm was -0.13 g/min (0.026; −0.18 to −0.08) compared to −0.04 g/min (0.033; −0.11, 0.03) in the placebo arm. The LS-Mean difference in uSFR (SE; 95% CI) between the incobotulinumtoxinA 100 U arm and the placebo arm of −0.09 g/min (0.031; −0.15 to −0.03) was statistically significant in favour of incobotulinumtoxinA 100 U (P = 0.004). In the EP (cycles 2, 3, and 4), similar mean changes in uSFR from study baseline to week 4 were observed for patient treated with incobotulinumtoxinA 100 U, although mean changes with reference to the baseline for each cycle were much smaller in magnitude (−0.03 to −0.06 g/min).

At week 4 of the MP, the LS-Mean patient GICS (SE; 95% CI) in the incobotulinumtoxinA 100 U arm was 1.25 (0.144; 0.97 to 1.53) compared to 0.67 (0.186; 0.30 to 1.04) in the placebo arm. The LS-Mean difference in GICS (SE; 95% CI) between the incobotulinumtoxinA 100 U arm and the placebo arm of 0.58 (0.183; 0.22 to 0.94) was statistically significant in favour of incobotulinumtoxinA 100 U (P = 0.002). In the EP (cycles 2, 3 and 4), similar mean GICS at week 4 was reported by patients treated with incobotulinumtoxinA 100 U to describe changes in sialorrhea since the previous injection.

At week 4 of the MP, the LS-Mean change in DSFS sum score (SE; 95% CI) in the incobotulinumtoxinA 100 U arm was −1.66 (0.234; −2.12 to −1.20) compared to −0.50 (0.296; −1.08 to 0.09) in the placebo arm; the LS-Mean difference in DSFS sum score (SE; 95% CI) between the incobotulinumtoxinA 100 U arm and the placebo arm was −1.17 (0.278; −1.71 to −0.72). In the EP (cycles 2, 3, 4), similar mean changes in DSFS sum scores for patients treated with incobotulinumtoxinA 100 U were observed with respect to study baseline.

At week 4 of the MP, larger mean (SD) decreases were observed in mROMP drooling scores in the incobotulinumtoxinA 100 U arm (−5.66 [6.16]) compared to the placebo arm (−1.00 [4.71]) were observed. In the EP (cycles 2, 3, 4), similar or larger mean changes in mROMP drooling scores for patients treated with incobotulinumtoxinA 100 U were observed with respect to study baseline.

No significant changes in HRQoL measured using the EQ VAS were observed during the MP or EP for patients treated with incobotulinumtoxinA 100 U or placebo.

Consistent differences of similar magnitudes in efficacy outcomes (uSFR, GICS, DSFS, and mROMP), but not in HRQoL, were observed between incobotulinumtoxinA 100 U and placebo treated patients at weeks 8 and 12 of the MP. For patients treated with incobotulinumtoxinA 100 U, similar magnitudes of change from study baseline were observed during each of the 3 additional 3 treatment cycles of the EP.

According to the clinical expert consulted by CADTH for this review, the LS-Mean differences in GICS and DSFS between the incobotulinumtoxinA 100 U and placebo arms observed during the MP of the study were clinically meaningful.

Harms Results

In the MP of the SIAXI study, AEs and serious AEs (SAEs) occurred with similar frequencies in the placebo (41.7% and 8.3%, respectively) and incobotulinumtoxinA 100 U (45.9% and 12.2%, respectively) arms; withdrawal due to AEs (WDAEs) were extremely rare (0% and 1.2%, respectively) and no deaths occurred. In the EP consisting of a 48-week follow-up period, only slightly higher rates of AEs and SAEs were observed in incobotulinumtoxinA 100 U treated patients (60.7% and 15.7%, respectively). During the EP, WDAEs occurred in 9.0% of patients treated with 100 U incobotulinumtoxinA, more than half of whom (4.5%) discontinued due to dry mouth. AEs of special interest (AESIs) considered by investigators as potentially related to toxin spread occurred in 6.8% of patients in the incobotulinumtoxinA 100 U arm but no placebo treated patients in the MP, as well as 13.5% of incobotulinumtoxinA 100 U treated patients in the EP. These AESIs were generally manageable in most patients. Dysphagia occurred in 4.5% of incobotulinumtoxinA treated patients in the EP. Dental-related AEs did not occur more frequently in patients treated with 100 U incobotulinumtoxinA compared with placebo.

Critical Appraisal

SIAXI was rigorously designed with no major risks of bias. Some areas of potential concern that may impact interpretation of the study results should be noted. There were imbalances between treatment arms in terms of some concomitants medications and therapies, most notably DBS. The clinical expert consulted by CADTH for this review stated that this imbalance was unlikely to impact the internal validity of the study, as patients were kept on the same therapy (medications and/or DBS) before and throughout the study. The study used unvalidated outcome measures with no evidence available to support validity, reliability and responsiveness to change; placebo effects were observed for all outcomes. Especially for categorical outcomes measured using Likert scales, like the GICS, the degree to which these constructs were sensitive in delineating true treatment responses from placebo effects was unclear. The study was overpowered for efficacy (based on effect sizes from a prior study of rimabotulinumtoxinB) because of the larger sample size required for safety evaluation, but still detected relatively small mean differences in efficacy outcomes between incobotulinumtoxinA 100 U and placebo. The clinical meaningfulness of differences of these magnitudes was uncertain in part because no evidence was available to suggest a MID for any of the outcome measures. Despite these caveats, consistent differences in favour of incobotulinumtoxinA were observed across all study outcomes with similar timing (weeks 4, 8, and 12 post-injection).

The characteristics of patients treated in SIAXI were generally similar to the Canadian context although there were no study sites in Canada. However, patients were mostly White, male, from only 2 countries (Germany and Poland), and almost all had sialorrhea secondary to either PD/AP or stroke. In addition, over the complete study (MP + EP) patients were followed and monitored very frequently over 64 weeks, and whether the study's findings are generalizable to patients with different levels of background care or less stringent dosing schedules is unclear. None of the efficacy outcomes used in SIAXI are used routinely in clinical practice and their clinical relevance, importance to patients, and correlation with HRQoL was not clear.

Indirect Comparisons

No indirect evidence was identified for this review. A feasibility assessment conducted by the sponsor also concluded that no data were currently available to inform an indirect treatment

comparison between incobotulinumtoxinA and other interventions, including injection of other BoNTs.

Other Relevant Evidence

One additional exploratory single-centre DB randomized controlled trial was summarized to provide additional evidence in patients with other neurologic conditions and to provide comparative evidence for incobotulinumtoxinA and onabotulinumtoxinA. Note that this study was not designed as a direct head-to-head comparison of these 2 BoNTs.

Description of Studies

The study by Restivo et al. recruited a consecutive series of patients (aged 18 to 75 years) with PD, stroke, TBI, ALS, and CP (N = 90) with severely disabling sialorrhea. The primary goal of the study was to assess the relationship between efficacy in reducing sialorrhea and number of glands injected; however, analyses of interest to this review included comparative efficacy assessment of incobotulinumtoxinA vs onabotulinumtoxinA and of BoNT efficacy in patients with different neurologic conditions. Patients were randomized to receive BoNT-A injections (either incobotulinumtoxinA or onabotulinumtoxinA) in different numbers of salivary glands (two, 3 or 4) resulting in a total dose received of 50 U, 75 U or 100 U. At baseline and 2 weeks post-injection, salivary production was measured by weighing of dental rolls placed in the patient's mouth for 5 minutes. The change in salivary production from baseline was evaluated on a Likert scale (0: no reduction, 1: 25% reduction, 2: 50% reduction, and 3: 75% reduction in salivary weight).

Efficacy Results

There was a clear pattern of dose response for both BoNT-A types, with Likert scores increasing along with increasing number of glands injected ($P < 0.001$), but no interaction between BoNT-A type and number of glands injected. The Likert scores of patients treated with the 2 BoNT-A types appeared to be similar, although the numerical data were not reported ($P = 0.12$). Subgroup analysis by etiology of sialorrhea in the overall population treated with all doses of BoNT-A (either incobotulinumtoxinA and onabotulinumtoxinA) suggested a potential difference in treatment effect by neurologic condition ($P < 0.001$).

Harms Results

Harms were not formally analyzed.

Critical Appraisal

The study by Restivo et al. was described in limited detail and there was significant uncertainty regarding its internal and external validity. Randomization was by number of glands injected rather than BoNT received, and so the comparative evidence from this study (incobotulinumtoxinA vs onabotulinumtoxinA) was potentially susceptible to bias and confounding. Furthermore, inability to account for imbalances in BoNT type administered to patients with different neurologic conditions (and vice versa) weakened analysis of either factor. Only 8 patients in the study were treated with the Health Canada–approved dose of incobotulinumtoxinA (100 U) and none of these had neurologic conditions different from those assessed in the SIAXI study. Thus, the study was unable to address the evidence gaps relating to the efficacy of incobotulinumtoxinA in patients with neurologic conditions other than PD/AP and stroke and to comparative efficacy vs other BoNT-A injections for this indication.

Economic Evidence

Cost and Cost-Effectiveness

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients with neurologic disorders who have chronic sialorrhea
Treatment	IncobotulinumtoxinA + SoC
Submitted price	IncobotulinumtoxinA, 50 U: $165.00 per single-use vial IncobotulinumtoxinA, 100 U: $330.00 per single-use vial
Treatment cost	The sponsor assumed that the annual cost of incobotulinumtoxinA treatment would be $1,073 if patients remained on therapy (assuming 3.25 administrations per year)
Comparators	SoC (consisting of basic non-pharmacological sialorrhea management, including physical aids, such as bibs, as well as speech language pathologist and occupational therapist consultations) OnabotulinumtoxinA + SoC
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	15 years
Key data sources	• SIAXI trial: IncobotulinumtoxinA + SoC compared to SoC • Assumption of equal clinical efficacy and safety based on a naive comparison: OnabotulinumtoxinA + SoC compared to IncobotulinumtoxinA + SoC
Submitted results	Based sequential analyses: • The ICER of incobotulinumtoxinA + SoC was $14,417 per QALY gained compared to SoC (incremental cost: $7,287, incremental QALY: 0.51) • OnabotulinumtoxinA + SoC was dominated (i.e., more costly and similarly effective) by IncobotulinumtoxinA + SoC.
Key limitations	• The analysis did not include all relevant comparators including treatments used off-label (e.g., anticholinergics). As such the cost-effectiveness of incobotulinumtoxinA compared to these treatments is unknown. • The model was not based on the natural history of sialorrhea or the underlying neurologic conditions patients eligible for incobotulinumtoxinA would have, and thus does not consider the implications of how worsening in the natural course of the underlying neurologic condition, or natural worsening in sialorrhea, could affect the cost-effectiveness of incobotulinumtoxinA. • The quality of life associated with sialorrhea severity is uncertain and likely to vary substantially based on the severity of the patient's underlying neurologic condition, which is expected to have a greater impact on quality of life than sialorrhea.

Component	Description
	• The sponsor's use of general population mortality is not reflective of patient's underlying neurologic conditions. Underestimating mortality results in an overestimate of the effectiveness of incobotulinumtoxinA. • SoC, conceptualized as placebo in the model, is not reflective of SoC in the Canadian context. SoC (assumed equal to placebo in the SIAXI trial) is assumed to consist of physical aids. The model incorporates discontinuation of SoC in the model, which is not reflective of Canadian practice. • The lack of robust direct or indirect evidence comparing onabotulinumtoxinA with incobotulinumtoxinA and SoC limits how informative the sequential analysis is.
CADTH reanalysis results	• CADTH undertook reanalyses to address limitations relating to: health state utility values; mortality of patient's underlying neurologic conditions; discontinuation of SoC; and, removing onabotulinumtoxinA from the sequential analysis. • Compared to SoC alone, the ICER for incobotulinumtoxinA + SoC is $67,239 per QALY. • For incobotulinumtoxinA to be considered cost-effective at a WTP threshold of $50,000 per QALY compared to SoC, a 30% price reduction would be required. • CADTH considered a scenario analysis with an assumption that incobotulinumtoxinA is equally effective as onabotulinumtoxinA, which suggested that incobotulinumtoxinA is less costly than onabotulinumtoxinA at the currently available prices.

LY = life year; QALY = quality-adjusted life-year; SoC = standard of care; WTP = willingness to pay.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the displacement of off-label botulinum toxin products by incobotulinumtoxinA was underestimated, the proportion of those eligible for pharmacological treatments who use them is expected to increase with the availability of an indicated sialorrhea treatment, off-label comparator costs were not incorporated in the analysis, the number of annual administrations was not aligned with the pharmacoeconomic analysis, the public coverage data used does not consider the age of the eligible population, and thus may be underestimated, and the epidemiological filtering approach may have underestimated the number of people eligible for incobotulinumtoxinA.

CADTH reanalyses included: assuming incobotulinumtoxinA displaces use of off-label botulinum toxin products; assuming 20% of those eligible for pharmacological treatments will use them; 3.25 administrations of incobotulinumtoxinA annually and assuming public coverage rates among those 65+. Based on the CADTH reanalyses, the budget impact from the introduction of incobotulinumtoxinA is expected to be $9,674,555 in Year 1, $10,405,678 in Year 2 and $11,451,543 in Year 3 with a 3-year total budget impact of $31,531,777.

The size of the eligible population remains a key source of uncertainty. Higher estimates of sialorrhea prevalence (i.e., assuming that the prevalence of sialorrhea used in the model applies to all of those with neurologic conditions, not just those with severe disease) increased the expected 3-year budget impact to $143 million. Restrictions on incobotulinumtoxinA availability by sialorrhea severity is also expected to decrease the budget impact.

CADTH

Canadian Drug Expert Committee (CDEC) Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Sally Bean, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Dr. Kerry Mansell, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Meeting date: July 21, 2021

Regrets: None

Conflicts of interest: None