

6.04 INCOBOTULINUMTOXIN A, Lyophilised powder for injection 100 units, Xeomin[®], MERZ AUSTRALIA PTY LTD.

1 Purpose of submission

- 1.1 The Category 2 submission requested a Section 100 (Botulinum toxin program), Authority Required (STREAMLINED) listing of incobotulinumtoxinA 100 units (U) for the treatment of chronic sialorrhea due to neurological disorders.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus standard medical management or standard of care (SoC)/placebo. The key components of the clinical issue addressed by the submission are summarised in Table 1.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Chronic sialorrhea in adults 18 years and older with neurological disorders including Parkinson's disease, atypical parkinsonism, traumatic brain injury and stroke; and children and adolescents aged 2 to 17 years with neurological disorders including cerebral palsy, traumatic brain injury and other developmental disorders.
Intervention	IncobotulinumtoxinA, purified Botulinum toxin type A, free from complexing proteins (Xeomin [®])
Comparator	Standard medical management (placebo)
Outcomes	Primary efficacy endpoints ^a : <ul style="list-style-type: none"> Change from baseline in unstimulated salivary flow rate (uSFR) Patients (or carers) Global Impression of Change Scale (GICS) entry Primary safety endpoints: <ul style="list-style-type: none"> Treatment emergent adverse events (TEAEs) overall and per injection cycle
Clinical claim	In adults ≥18 years: <ul style="list-style-type: none"> IncobotulinumtoxinA is superior to standard of care/placebo in reducing the severity and frequency of salivary flow in patients with chronic, troublesome sialorrhea due to neurological disorders, including Parkinson's disease, atypical parkinsonism, traumatic brain injury and stroke. IncobotulinumtoxinA is inferior to placebo in terms of safety. In children and adolescents aged 2–17 years: <ul style="list-style-type: none"> IncobotulinumtoxinA is superior to standard of care/placebo in reducing the severity and frequency of salivary flow in patients with chronic, troublesome sialorrhea due to neurological disorders, including cerebral palsy, traumatic brain injury and other developmental disorders. IncobotulinumtoxinA is inferior to placebo in terms of safety

Source: Table 1.1.1, p2 of the submission; p76 of the submission.

^a Data for both co-primary endpoints were collected for children and adolescents (6–17 years) as well as adults (≥ 18 years). The uSFR data was not collected for the 2–5 years age group.

2 Background

Registration status

- 2.1 IncobotulinumtoxinA was TGA registered in November 2023 for use in chronic sialorrhea in adults (≥ 18 years) and children and adolescents (aged 2–17 years). IncobotulinumtoxinA 100U was first registered on the Australian Register of Therapeutic Goods (ARTG) on 21st March 2014.
- 2.2 The TGA indications for incobotulinumtoxinA for adults are for the treatment of:
- Cervical dystonia (spasmodic torticollis),
 - Blepharospasm,
 - Spasticity of the upper limb,
 - Chronic sialorrhea due to neurological disorders.
 - Upper facial lines:
 - Glabellar frown lines,
 - Lateral periorbital lines (crow's feet),
 - Horizontal forehead lines.
- 2.3 The TGA indications for incobotulinumtoxinA for children and adolescents aged 2 to 17 years are for the symptomatic treatment of:
- Chronic sialorrhea due to neurological/neurodevelopmental disorders,
 - Spasticity of the lower and/or upper limbs.

Previous PBAC consideration

- 2.4 The PBAC has not previously considered incobotulinumtoxinA for this indication.
- 2.5 The PBAC has previously recommended incobotulinumtoxinA for the treatment of blepharospasm, spasmodic torticollis or cervical dystonia, and moderate to severe spasticity of the upper limb/s following an acute event in adults (paragraph 7.1, IncobotulinumtoxinA, Public Summary Document [PSD], July 2014 PBAC Meeting; paragraph 6.1, IncobotulinumtoxinA, PSD, November 2019 PBAC Meeting). IncobotulinumtoxinA is not PBS listed for any indications in children and adolescents.

For more detail on PBAC's view, see Section 7 PBAC outcome.

3 Requested listing

- 3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

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MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
INCOBOTULINUMTOXINA					
IncobotulinumtoxinA 100 units injection, 1 vial	\$379.17	1	1	0	Xeomin

Restriction Summary [NEW 1] / Treatment of Concept: [NEW 2]	
Category / Program: <input checked="" type="checkbox"/> Section 100 – Botulinum Toxin Program (Code MF)	
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners	
Restriction type: <input checked="" type="checkbox"/> Authority Required (Streamlined) (new code)	
<i>Caution: Contraindications to treatment include known sensitivity to botulinum toxin.</i>	
<i>Administrative Advice: The units used to express the potency of botulinum toxin preparations currently available for PBS subsidy are not equivalent.</i>	
Episodicity: Chronic	
Severity: N/A	
Condition: Sialorrhea	
Indication: Chronic sialorrhea	
Treatment phase: Initial	
Clinical criteria:	
Patient must have be initiating treatment with a drooling severity and frequency scale (DSFS) score of at least 6; OR	
Patient must be continuing treatment with improvement in the DSFS score of at least 1 point from baseline as assessed by the treating clinician.	
AND	
Clinical criteria:	
Patient must have Parkinson's disease; OR	
Patient must have atypical Parkinson's; OR	
Patient must have traumatic brain injury; OR	
Patient must have chronic sialorrhea following an acute event.	
Population criteria:	
Patient must be at least 18 years of age.	
Treatment criteria:	
Must be treated by a neurologist; or	
Must be treated by a rehabilitation specialist; or	
Must be treated by a geriatrician; or	
Must be treated by an ear, nose and throat otolaryngologist surgeon; or	
Must be treated by a plastic surgeon	

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Administrative advice:

For the purposes of administering this restriction, the Drooling Score is defined as the score that equals the sum of the Severity and Frequency sub-scores.

Drooling Severity Scale

1. Never drools, dry
2. Mild-drooling, only lips wet
3. Moderate- drool reaches the lips and chin
4. Severe- drool drips off chin & onto clothing
5. Profuse- drooling off the body and onto objects (furniture, books)

Drooling Frequency Scale

1. No drooling
2. Occasionally drools
3. Frequently drools
4. Constant drooling

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
INCOBOTULINUMTOXINA					
incobotulinumtoxinA, 100 units injection, 1 vial	New	1	1	0	Xeomin
Restriction Summary [NEW 3] / Treatment of Concept: [NEW 4]					
Category / Program: <input checked="" type="checkbox"/> Section 100 – Botulinum Toxin Program (Code MF)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required (Streamlined) (new code)					
Caution: Contraindications to treatment include known sensitivity to botulinum toxin.					
Administrative Advice: The units used to express the potency of botulinum toxin preparations currently available for PBS subsidy are not equivalent.					
Episodicity: Chronic					
Severity: N/A					
Condition: Sialorrhea					
Indication: Chronic sialorrhea					
Treatment phase: Initial					
Clinical criteria:					
Patient must have be initiating treatment with a drooling severity and frequency scale (DSFS) score of at least 6; OR					
Patient must be continuing treatment with improvement in the DSFS score of at least 1 point from baseline as assessed by the treating clinician.					
AND					
Clinical criteria:					
Patient must have cerebral palsy; OR					
Patient must have traumatic brain injury; OR					
Patient must have developmental disorder OR					
Population Criteria:					
Patient must be aged from 2 to 17 years inclusive.					
Treatment criteria:					
Must be treated by a neurologist; or					
Must be treated by a rehabilitation specialist; or					
Must be treated by a paediatrician; or					
Must be treated by an ear, nose and throat otolaryngologist surgeon; or					

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Must be treated by a plastic surgeon
Treatment criteria:
Treatment must be guided by ultrasound.
<p>Administrative advice: For the purposes of administering this restriction, the Drooling Score is defined as the score that equals the sum of the Severity and Frequency sub-scores as follows:</p> <p><i>Drooling Severity Scale</i></p> <ol style="list-style-type: none"> 1. Never drools, dry 2. Mild-drooling, only lips wet 3. Moderate- drool reaches the lips and chin 4. Severe- drool drips off chin & onto clothing 5. Profuse- drooling off the body and onto objects (furniture, books) <p><i>Drooling Frequency Scale</i></p> <ol style="list-style-type: none"> 1. No drooling 2. Occasionally drools 3. Frequently drools 4. Constant drooling

- 3.2 The proposed dispensed price for maximum quantity (DPMQ) of \$379.17 per vial was the same as the current price of other PBS listings of incobotulinumtoxinA.
- 3.3 The submission requested listing incobotulinumtoxinA under the Section 100 (Botulinum toxin program) as an Authority Required (Streamlined) restriction type. The evaluation considered that this was reasonable. Previous PBS listings of incobotulinumtoxinA for blepharospasm, spasmodic torticollis or cervical dystonia, and moderate to severe spasticity of the upper limbs following an acute event also have Authority Required (Streamlined) listings.
- 3.4 The requested PBS listing does not align with the proposed treatment algorithm, which positions incobotulinumtoxinA in the third-line setting following non-pharmacological/conservative measures and oral or topical anticholinergics (see paragraph 4.8).
- 3.5 The requested PBS listing was narrower than the TGA indication for chronic sialorrhea as it requires participants to have a Thomas-Stonell and Greenberg Drooling Severity and Frequency Scale (DSFS) score of ≥ 6 which is not a requirement of the TGA indication.
- 3.6 In adults, the requested DSFS requirements were broader than the inclusion criteria in the SIAXI trial. The trial required participants to have a DSFS score of ≥ 6 , at least 2 points for each item of the DSFS, and at least 3 points on the modified Radboud Oral Motor Inventory for Parkinson’s disease (mROMP), Section III ‘Drooling’, Item A. However, the requested PBS listing only required patients to have a DSFS score of ≥ 6 . In children, the SIPEXI trial did not use the DSFS, instead the inclusion criteria required patients to have a modified Teacher’s Drooling Scale (mTDS) score of ≥ 6 .
- 3.7 The DSFS consists of 2 subscales, a 4-point Likert scale for ‘drooling frequency’ and a 5 point Likert scale for ‘drooling severity’. The DSFS is the sum of the 2 subscales. The

highest possible score is 9. The severity and frequency of drooling was evaluated 'over the past week' in the SIAXI trial.

3.8 The ESC noted that the use of DSFS in the restriction may be associated with some issues, including:

- The DSFS lacks psychometric and statistical/clinical validation (Nascimento et al. 2021)^{1,2}.
- As noted in the submission, the DSFS is not widely used in clinical practice.
- The DSFS is designed to assess both the severity and frequency of sialorrhea. However, it does not capture the impact of drooling on daily activities, quality of life, or emotional distress.

Thus, clinicians may be more likely to rely on clinical judgment to determine severity and treatment improvement rather than using a formal rating scale. The Pre-Sub-Committee Response (PSCR) maintained that the inclusion of DSFS in the restriction was appropriate and aligned with the clinical evidence. The PSCR also stated that it was willing to accept guidance and amend the wording of the restriction; however, cautioned that the removal of the DSFS criterion may lead to significant growth in the eligible patient population. The ESC considered that the lack of psychometric and statistical/clinical validation was the primary concern related to the inclusion of the DSFS in the proposed restriction. However, the ESC considered the scale was likely to be a useful and practical tool and would assist prescribers in ensuring the PBS eligibility of their patients. Therefore, the ESC considered its inclusion was likely reasonable. The DUSC also considered the inclusion of the DSFS to be reasonable. The ESC considered that the DSFS definition provided as administrative advice, as suggested by the Secretariat (shown above), was appropriate and would simplify the process of using the scale for prescribers.

3.9 A continuing supply restriction was not proposed in the submission. Without a continuing supply restriction, patients are only eligible to continue treatment if their DSFS score remained ≥ 6 . Patients experiencing significant improvement in their DSFS score would no longer be able to access incobotulinumtoxinA treatment. This was inconsistent with the submission's proposed treatment algorithm which stated that patients could continue treatment every 16 weeks if an improvement in DSFS score of 1 point or greater had been observed from treatment initiation. The economic model also assumed that patients who had a DSFS score that fell below 6 continued treatment. The PSCR agreed to the inclusion of a continuing treatment phase and proposed criteria specifying that patients can continue treatment if they experience a 1 point improvement in DSFS while on treatment. Although a continuing phase

¹ Nascimento D, Carmona J, et al. (2021) Drooling rating scales in Parkinson's disease: A systematic review. *Parkinsonism & Related Disorders*. 2021 Oct 1;91:173-80.

² Report Viewer; NINDS Common Data Elements: [https://www.commondataelements.ninds.nih.gov/report-viewer/23376/Drooling%20Severity%20and%20Frequency%20Scale%20\(DSFS\)](https://www.commondataelements.ninds.nih.gov/report-viewer/23376/Drooling%20Severity%20and%20Frequency%20Scale%20(DSFS))

restriction was proposed in the PSCR, a phase agnostic restriction was proposed by the Secretariat through the addition of clinical criteria specifying that patients can initiate or continue treatment based on their DPSC score. This was consistent with the existing PBS listings of botulinum toxin medicines. The ESC considered that the inclusion of a criterion requiring an improvement in a DSFS score to continue treatment was likely reasonable.

3.10 Whether a one-unit increase in DSFS was sufficient to be regarded as a response to incobotulinumtoxinA for treatment continuation every 16 weeks was uncertain as:

- A minimal clinically important difference (MCID) was not proposed by the submission;
- Clinicians may rely on clinical judgment to determine severity and treatment improvement rather than using a formal rating scale, such as the DSFS; and
- The SIAXI and SIPEXI trials defined the response to incobotulinumtoxinA in terms of a change in patient and carer's Global Impression of Change Scale (GICS) ≥ 1 , not DSFS.

The PSCR argued that the DSFS (i.e. improved drooling control) in the SIAXI trial was correlated with improved quality of life (EQ-5D-3L). The response also noted that DSFS scores correlated with quantitative measures of drooling, including bib count and bib weight.³ Additionally, the PSCR claimed that given that improvement in DSFS outcome scores in SIAXI exceeded a one-point decrease, it was reasonable to assume there was a relevant improvement in patient quality of life that was sufficient to define the response threshold. The submission did not formally assess whether the correlation between DSFS and the EQ-5D-3L was significant. However, taking into account the clinical trial outcomes, existing literature and results presented in the submission, the ESC considered a one-unit increase in DSFS was likely to be a reasonable response threshold.

3.11 The requested PBS listing for adults included patients with 'chronic sialorrhea following an acute event'. An acute event was not explicitly defined in the submission. Upon request for clarification from the evaluation, the PSCR provided the following definition of an acute event: 'a brain stroke, traumatic brain injury, or any event that causes chronic sialorrhea that is not the result of a chronic disease.' The SIAXI trial for adults included a limited number of participants with traumatic brain injuries (TBIs).

3.12 The requested PBS listings required treatment to be guided by ultrasound for children and adolescents but not for patients 18 years or older. Although the TGA indication does not include such a requirement, the submission included the cost of ultrasound in both the economic and financial models for all patients regardless of age. The ESC noted that for the SIAXI trial, each treatment was administered in four injections into

³ Sforza, Elisabetta, et al. "Drooling outcome measures in paediatric disability: a systematic review." *European Journal of Pediatrics* 181.7 (2022): 2575-2592.

the bilateral parotid and submandibular salivary glands, guided by either ultrasound or anatomical landmarks. at the discretion of the investigator. In the SIPEXI trial, ultrasound guidance was used for all injections in the safety evaluation set (SES) population. The ESC considered that for adult patients, injections were more commonly guided by anatomical landmarks than ultrasound in the Australian clinical setting. However, the ESC considered the proportion of children that would require ultrasound remained uncertain.

- 3.13 The requested PBS listing for adults included chronic sialorrhea related to Parkinson's disease, atypical Parkinson's disease, traumatic brain injury, or following an acute event. For children, the requested PBS listing included cerebral palsy, traumatic brain injury, and developmental disorders. The submission stated that a survey of Australian specialists in neurological conditions identified additional conditions unrepresented by the pivotal clinical trials (SIAXI trial for adults and SIPEXI trial for children and adolescents) that could cause chronic sialorrhea, including adult cerebral palsy, motor neurone disease, hypoxic brain injury, Alzheimer's disease, multiple sclerosis, and generalised developmental delay or genetic disorders. The ESC noted that the submission suggested that it may be appropriate to extend the listing criteria to include patient groups not covered in the pivotal trials. The ESC advised that the extension of the listing to include patients outside the patient groups studied in SIAXI and SIPEXI trials was likely not reasonable. However, this issue remains for PBAC consideration. See paragraph 6.113 for further information.
- 3.14 In addition, the PBAC is asked to consider whether children who have received treatment for chronic sialorrhea due to cerebral palsy or developmental disorders should be allowed to continue treatment into adulthood. See paragraph 6.113 for further information.
- 3.15 To ensure there will be access to the required MBS items, a MSAC application for the administration of incobotulinumtoxinA for chronic sialorrhea is required. The pre-PBAC response stated that an application to MSAC would be lodged late November 2024.

For more detail on PBAC's view, see Section 7 PBAC outcome.

4 Population and disease

- 4.1 Sialorrhea (i.e. excessive salivation or drooling) refers to the overflow of saliva beyond the lip margin. This condition is typically normal in infants and generally diminishes between 15 and 36 months as they develop salivary control. However, it is considered abnormal beyond an age of 4 years (Lakraj et al. 2013)⁴. Excess saliva may also travel backwards down the pharynx.

⁴ Lakraj AA, Moghimi N, Jabbari B. (2013) Sialorrhea: Anatomy, Pathophysiology and Treatment with Emphasis on the Role of Botulinum Toxins. *Toxins* [Internet]. 5(5):1010-31

- 4.2 Sialorrhea can result from either the overproduction of saliva or its accumulation in the front part of the mouth due to poor swallowing. This condition is often linked to neuromuscular disorders such as Parkinson's disease, stroke, or cerebral palsy. Other causes include hypersecretion due to medication side effects or gastroesophageal reflux disease, and anatomical issues like an enlarged tongue, oral incompetence, or dental misalignment.
- 4.3 In children, sialorrhea is frequently associated with physical disabilities such as infantile cerebral palsy, various neurodevelopmental disorders, intellectual disabilities, metabolic conditions, and neurodegenerative diseases. It can also be a non-specific sign of disturbed oral-motor control. The overall prevalence of chronic sialorrhea among children and adolescents was found to be approximately 0.6% (Fairhurst et al. 2011)⁵.
- 4.4 The adverse effects of sialorrhea can significantly impact the quality of life, leading to social isolation, unclear speech, and skin irritation around the mouth. More severe consequences include dehydration, choking, aspiration, and pneumonia, which can increase morbidity and mortality (Hockstein et al. 2004, Scully et al. 2009, Akbar et al. 2015)^{6,7,8}. Sialorrhea can also have negative effects on communication, eating, and social interactions (Leibner et al. 2010)⁹.
- 4.5 The submission noted multiple methods that could be used to assess the presence and severity of sialorrhea in individuals with neurological disorders. These included descriptive rating scales to evaluate the severity and frequency of drooling and considering patients' medical history, including the impact of drooling on their health, such as recurrent skin or respiratory infections, dental health, eating and drinking difficulties, oral speech problems, and overall quality of life. The trials for adults (SIAXI) and children and adolescents (SIPEXI) used the DSFS and mTDS, respectively, to measure the severity and frequency of chronic sialorrhea.
- 4.6 The submission noted that current treatments for sialorrhea in both adults and children with neurological disorders included both pharmacological and non-pharmacological therapies. Conservative approaches could involve behavioural or physical management, including: changes to posture, wiping of the mouth, intentional swallowing, or other oral motor exercises.
- 4.7 Behavioural modifications, such as using cues to increase swallowing or wiping of the mouth or physical therapy using games and sensory toys or devices, could be used to

⁵ Fairhurst C, Cockerill H (2011) Management of drooling in children. *Arch Dis Child Educ Pract Ed.* 96(1):25-30

⁶ Hockstein NG, Samadi DS, et al. (2004) Sialorrhea: a management challenge. *Am Fam Physician.* 69(11):2628-34.

⁷ Scully C, Limeres J, et al. (2009) Drooling. *Journal of Oral Pathology & Medicine.* 38(4):321-7.

⁸ Akbar U, Dham B, et al. (2015) Incidence and mortality trends of aspiration pneumonia in Parkinson's disease in the United States, 1979-2010. *Parkinsonism Relat Disord.* 21(9):1082-6.

⁹ Leibner J, Ramjit A, et al. (2010) The impact of and the factors associated with drooling in Parkinson's disease. *Parkinsonism Relat Disord.* 16(7):475-7.

improve sensory awareness, muscle control, and oral motor function, especially among children.

- 4.8 The proposed treatment algorithm states that non-pharmaceutical/conservative measures such as behavioural modification, physical therapy and oral devices, are used in the first-line setting, followed by either oral or topical anticholinergics (mainly benzhexol hydrochloride, benztropine, or glycopyrronium bromide (glycopyrrolate)) in the second line setting and botulinum toxin injections are then used in the third-line setting. As no anticholinergics or botulinum toxin type A injections (Dysport®, Botox®) have been TGA-approved for treating sialorrhea in Australia, their use is off-label. The proposed algorithm states that incobotulinumtoxinA would replace botulinum toxin type A injections (third-line setting).
- 4.9 The submission did not elaborate on why incobotulinumtoxinA could not be considered as an alternative treatment to non-pharmacological/conservative management options or off-label anticholinergics. IncobotulinumtoxinA was presented as both the first- and second-line treatment options when applying for approval from the National Health Service (NHS, UK). In this regard, the NICE¹⁰ committee considered incobotulinumtoxinA as:
- An alternative first-line treatment to non-pharmacological management such as bibs, speech and language therapy and occupational therapy (referred to as standard care by the company) and to anticholinergics, and
 - As an alternative second-line treatment to standard care.
- 4.10 The submission noted that anticholinergic drugs have a short duration of effect and must be used daily or multiple times per day. The submission also noted that anticholinergics could have undesirable side effects, including dry mouth, constipation, urinary retention, blurred vision, hyperactivity, irritability, confusion, and drowsiness, and are contraindicated in patients with glaucoma, obstructive uropathy, gastrointestinal motility disorders, and myasthenia gravis. These medications are often poorly tolerated in elderly patients with multiple comorbidities (Hockstein et al. 2004)¹¹.
- 4.11 Non-pharmacological options include surgery or radiation, such as denervation or removal of salivary glands, or ligation or relocation of salivary ducts. These surgical interventions are highly invasive and can have lasting impacts on dental and oral health. Surgery is generally considered for severe cases when other treatments have failed or are inappropriate. The submission noted that radiation of the salivary glands was rarely used and typically reserved for elderly patients who cannot tolerate surgery or medical therapies.

¹⁰ NICE (2019) Xeomin (botulinum neurotoxin type A) for treating chronic sialorrhea, technology appraisal guidance, published: 9 October 2019. www.nice.org.uk/guidance/ta605

¹¹ Hockstein NG, Samadi DS, et al. (2004) Sialorrhea: a management challenge. *Am Fam Physician*. 69(11):2628-34

- 4.12 IncobotulinumtoxinA is injected into the parotid and submandibular glands on both sides, totalling 4 injections per treatment. The dose is divided in a 3:2 ratio between the parotid and submandibular glands. The submission noted that the involved salivary glands could be localised using anatomic landmarks or ultrasound guidance. Children and adolescents may receive general anaesthesia to administer incobotulinumtoxinA.
- 4.13 For adults, the recommended and total maximum dose per treatment session is 100U for adults. Doses in children and adolescents are administered by body weight, and the recommended maximum dose per treatment session is 75U. Due to the lack of data, no dosing recommendations were made for children weighing <12 kg.
- 4.14 The submission noted that treatment intervals should be determined based on the actual clinical needs of the individual patient, and repeating treatment more frequently than every 16 weeks was not recommended. This applied to both adults and children and adolescents.

For more detail on PBAC's view, see Section 7 PBAC outcome.

5 Comparator

- 5.1 The submission nominated standard medical management (also referred to as standard of care, SoC in the submission) as the main comparator. The submission stated that this would consist of any conservative/non-pharmacological management strategies and includes the use of bibs and other clothing to catch saliva, behavioural management such as intentional swallowing or wiping of saliva, and physical therapy such as posture adjustment, oral motor exercises or oral strengthening devices. The placebo arms in the SIAXI trial (adults) and the SIPEXI trial (children and adolescents) were used to represent SoC in the submission.
- 5.2 The main arguments provided by the submission in support of this nomination were:
- There are no treatments for sialorrhea currently listed on the PBS.
 - While anticholinergic medications can be used to treat sialorrhea, they are not currently TGA-approved for this indication in Australia, making their use off-label. Furthermore, there is a lack of clinical evidence supporting the use of anticholinergics for treating sialorrhea in individuals with neurological disorders, and due to their off-label status, data on their effectiveness and safety is limited.
 - Surgical removal of salivary ducts, denervation, or radiation therapy are generally considered to be the last-resort treatments for severe sialorrhea. These highly invasive methods could result in permanent or long-lasting effects, making them unsuitable comparators for incobotulinumtoxinA.
- 5.3 The evaluation considered that the choice of standard medical management or SoC as the comparator may be reasonable; however, it does not align with the proposed treatment algorithm which proposed that incobotulinumtoxinA would replace

botulinum toxin type A injections (third-line setting). Further, although no anticholinergics are TGA approved for the treatment of chronic sialorrhea, several have unrestricted PBS listings and are used in clinical practice. Despite the side effects and poor tolerance that may be associated with long-term use, it may be appropriate to consider short-term/intermittent use of anticholinergics as a potential comparator.

For more detail on PBAC's view, see Section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (6) and 1 organisation via the Consumer Comments facility on the PBS website. The comments described the effectiveness of incobotulinumtoxinA in those with chronic sialorrhea in reducing salivary production. The comments noted that for some patients, sialorrhea can be a debilitating condition and that effective treatment and symptom control was associated with a significant improvement to the quality of life of patients. The input noted that incobotulinumtoxinA was associated with adverse side effects, including flu-like symptoms, excessive dry mouth and swallowing difficulties; however, considered these to be manageable. The input considered that the cost of incobotulinumtoxinA was a barrier to treatment and that its PBS listing would improve accessibility.

6.3 The PBAC acknowledged the input from Motor Neurone Disease (MND) Australia expressing support for listing incobotulinumtoxinA on the PBS for those with chronic sialorrhea. MND Australia noted that sialorrhea is a life-altering and serious health issue and is often described by people living with MND as their most troubling and distressing symptom. MND Australia noted that there remains a high clinical need for additional treatments for patients with chronic sialorrhea. Of the treatments available, many have significant side effects and are associated with high costs, as they are not PBS listing. MND Australia considered that effective management and treatment would reduce the likelihood of serious complications associated with chronic sialorrhea, such as choking, disturbed sleep and aspiration pneumonia. The PBAC noted that MND Australia stated that botulinum toxin injections were associated with adverse side effects, including dry mouth or worsening dysphagia and highlighted the importance that the dosage and administration was conducted by expert practitioners.

Clinical trials

6.4 The submission was based on 2 head-to-head randomised controlled trials comparing incobotulinumtoxinA to the SoC (placebo):

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- SIAXI trial (N=184) enrolled adults with chronic sialorrhea and neurological disorders and compared incobotulinumtoxinA 75U (n=74), and incobotulinumtoxinA 100U (n=74) to placebo (n=36) in patients with a baseline DSFS score ≥ 6 .
- SIPEXI trial (N=256) enrolled children and adolescents with chronic sialorrhea and neurological or developmental disorders and a baseline mTDS ≥ 6 . Dosing was weight-based:
 - 2–5 years age group: incobotulinumtoxinA (n= 36).
 - 6–17 years age group: incobotulinumtoxinA (n=148) to placebo (n=72).

- 6.5 The 2–5 years age group in the SIPEXI trial did not have a placebo control group for ethical reasons.
- 6.6 The open-label extension phase of the SIAXI trial (N=173) consisted of two arms, incobotulinumtoxinA 75U (n=84) and incobotulinumtoxinA 100U (n=89).
- 6.7 The open-label extension phase of the SIPEXI trial (N=247) was a single arm study, with all participants eligible for the extension phase receiving incobotulinumtoxinA treatment.
- 6.8 Details of the trial associated publications presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
SIAXI (NCT02091739)	Prospective, randomized, double-blind, placebo controlled, parallel-group multicenter study, with an extension phase of dose-blinded active treatment, to investigate the efficacy and safety of two dose levels of NT 201 in treating chronic troublesome sialorrhea in various neurological conditions.	CSR, May 2017
	Jost, WH., et al. SIAXI: Placebo-controlled, randomized, double-blind study of incobotulinumtoxinA for sialorrhea.	Neurology 2019; 92; e1982-e1991
	Jost, WH., et al. Long-term incobotulinumtoxinA treatment for chronic sialorrhea: Efficacy and safety over 64 weeks.	Neurology 2020; 70; 23-30
SIPEXI (NCT02270736)	Prospective, randomized, double-blind, placebo controlled, parallel-group, multicenter study with an open-label extension phase to investigate the efficacy and safety of NT 201 in the treatment of children and adolescents (2–17 years) with chronic troublesome sialorrhea associated with neurological disorders, and/or intellectual disability.	CSR, April 2020
	Berweck, S. et al. Placebo-Controlled Clinical Trial of IncobotulinumtoxinA for Sialorrhea in Children SIPEXI.	Neurology 2021; 97(14); e1425-36

Source: Table 2.2.2, pp28-29 of the submission.

Note: NT 201 denoted incobotulinumtoxinA.

- 6.9 The key features of the direct randomised trials are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design / duration	Bias	Patient population	Key Outcomes	Use in modelled evaluation
SIAXI ^a	184 adults (incobotulinumtoxinA 75U: 74; incobotulinumtoxinA 100U: 74; placebo: 36)	P, R, DB, PC, MC MP: 16 ± 2 weeks OLE: 56–72 weeks	Low	Adults (≥18 years) with chronic sialorrhea associated with neurological disorders ^b	Co-primary: uSFR at week 4 ^c ; GICS at week 4 ^d . Secondary and additional: uSFR: change from baseline to week 8 and 12; Participant's/Carer's GICS entry at weeks 1, 2, 8, and 12; Change in DSFS, EQ-5D-3L, Safety	DSFS: transition probabilities across the 3 severity-based health states EQ-5D-3L: Utilities
SIPEXI	36 children aged 2–5 years old (incobotulinumtoxinA 100U: 36) 220 children/adolescents aged 6-17 years old (incobotulinumtoxinA 100U: 148; placebo: 72)	P, R, DB, PC, MC MP: 16 ± 2 weeks OLE: 56–72 weeks	Low	Children and adolescents (2–17 years) with chronic sialorrhea associated with neurological/developmental disorders ^e	Co-primary: uSFR at week 4 ^c ; GICS at week 4 ^d . Secondary and additional: mTDS, uSFR: change from baseline to week 8 and 12; GICS at Week 8 and 12; Safety	uSFR used to indirectly impute ^f DSFS, which was used to estimate transition probabilities across health states.

Source: Compiled during the evaluation based on pp36-50 of the submission.

DB = Double-blind; DSFS = Drooling severity and frequency scale; EQ-5D-3L = EuroQol 5-dimensional 3-level; GICS = global impression of change scale; MC = multicentre; MP = Main phase; mTDS = modified Teacher's Drooling Scale; OLE = Open label extension; P = Prospective; PC = Placebo-controlled; R = Randomised; uSFR = unstimulated salivary flow rate; 75U = 75 units; 100U = 100 units.

^a The trial interventions included incobotulinumtoxinA 75U and incobotulinumtoxinA 100U. Only incobotulinumtoxinA 100U was considered in this submission.

^b Parkinson's disease, atypical parkinsonism, stroke and traumatic brain injury.

^c Change from baseline to Week 4; Measured by weighing of dental rolls soaked with saliva over 5 minutes and repeated after 30 minutes; also measured at Weeks 4, 8, 12 and 16 in the MP and Weeks 20, 32, 36, 48, 52, and 64 of OLE.

^d Reported by subjects and carers compared to their baseline sialorrhea, measured weekly.

^e Cerebral palsy, traumatic Brain Injury, and developmental disorders.

^f DSFS scores for the SIPEXI participants were imputed by applying the ratio of the difference between the uSFR and DSFS scores in the SIAXI trial to the uSFR scores in the SIPEXI trial; uSFR was not collected in the 2–5 years age group.

6.10 The main phase of the SIAXI and SIPEXI trials was 16 weeks, which was not adequate to capture long-term outcomes, especially quality of life and adverse events. Additionally, there is potential for the treatment effect of incobotulinumtoxinA to wane over time after repeated injections.¹²

Adults

6.11 The treatment regimen for patients in the incobotulinumtoxinA 100U arm of the SIAXI trial was consistent with *the regimen* recommended in the incobotulinumtoxinA TGA product information (PI). As the regimen in the incobotulinumtoxinA 75U arm was not consistent with the incobotulinumtoxinA TGA PI these data were not presented in the evaluation. The incobotulinumtoxinA 75U arm of the SIAXI trial did not achieve

¹² Lin YC, Wu WT, et al. (2018) Comparative effectiveness of botulinum toxin versus non-surgical treatments for treating lateral epicondylitis: a systematic review and meta-analysis. *Clinical Rehabilitation*. 2018 Feb;32(2):131-45.

statistical significance for any of the co-primary or secondary endpoints, compared to the placebo arm. Consequently, the TGA Evaluator concluded that the available evidence did not support the incobotulinumtoxinA 75U dose-regimen for the proposed indication (TGA AusPAR for incobotulinumtoxinA).

- 6.12 The SIAXI trial¹³ included adults diagnosed with idiopathic or familial Parkinson's disease (70.7%), atypical parkinsonism (such as multiple system atrophy, progressive supranuclear palsy, or corticobasal degeneration) (8.7%), stroke (19.0%), or TBI (2.7%). The trial included only 3 TBI participants (one in the placebo arm and 2 in the incobotulinumtoxinA arm).
- 6.13 There were differences between the SIAXI trial inclusion criteria and the clinical criteria in the requested PBS listing (see paragraph 3.6); however, the inclusion of a DSFS score ≥ 6 in the requested initial treatment phase restriction aligned with the inclusion criteria.
- 6.14 There were some differences between patients in the incobotulinumtoxinA 100U and placebo arms in terms of sex, age, concomitant diseases and concomitant treatments. However, these differences were considered unlikely to bias the results.
- 6.15 The co-primary outcomes of the SIAXI trial were unstimulated Salivary Flow Rate (uSFR) and GICS at Week 4. Secondary outcomes included the change in uSFR from baseline to week 8 and 12, subject/carer GICS entry at weeks 1, 2, 8, and 12, GICS at Week 8 and 12, EQ-5D-3L, DSFS, and safety.
- 6.16 The PBAC has not previously considered uSFR, GICS or DSFS. The uSFR measures the quantity of saliva produced by the salivary glands without any external stimulation, typically collected over a specific period. The GICS measures perceived change in a patient's condition post-treatment. Both patients and caregivers rate overall functioning compared to their state before the last treatment, using a 7-point Likert scale from -3 (very much worse) to +3 (very much improved). The DSFS assesses drooling through two domains: the Drooling Severity Scale and the Drooling Frequency Scale. The Severity Scale ranges from 1 (never drooling) to 5 (profuse drooling), while the Frequency Scale ranges from 1 (no drooling) to 4 (constant drooling).
- 6.17 The submission used DSFS as the main clinical criterion in the requested PBS listing to determine eligibility for treatment (i.e. DSFS ≥ 6), to determine improvement due to treatment with incobotulinumtoxinA 100U, including in the proposed treatment algorithm for continuing treatment, and to define severity states for use in the economic model. The DSFS was associated with a number of issues (see paragraph 3.8).

¹³ While the submission primarily focused on the characteristics of the incobotulinumtoxinA 100U and placebo arms based on the SIAXI trial, it also included the baseline characteristics of the incobotulinumtoxinA 75U arm.

- 6.18 The submission stated that there were no established or validated MCIDs for sialorrhoea treatment in any of the outcomes measured in the SIAXI trial. However, the submission stated that the SIAXI trial was powered to detect a mean change (SD) of 0.05 (0.22) g/min in uSFR and a mean change (SD) of 1.0 (1.93) points in GICS score, which the submission claimed were ‘statistically significant differences’ between treatment and placebo. The submission therefore proposed the following MCIDs: uSFR = 0.05 g/min, GICS score = 1.0 point. A MCID for DSFS was not available or proposed by the submission. The submission stated that the proposed MCIDs were taken from study protocols. The protocols were not provided with the submission and therefore the methodology and reliability of the proposed MCIDs could not be validated during the evaluation. The SIAXI and SIPEXI clinical trial protocols were provided with the PSCR. The PSCR maintained that basing MCIDs on clinical trial protocols was in accordance with the PBAC Guidelines (v5.0). The SIAXI trial protocol stated that the trial was powered to have a 95% probability of detecting a difference in mean change in uSFR at Week 4 between the incobotulinumtoxinA and placebo arms of 0.246 g/min, and a difference in mean GICS scores at Week 4 of 0.955.
- 6.19 With regards to the GICS, the ESC noted that Mercadante et al 2019¹⁴ reported for advanced cancer patients a mean change of at least 1.0 point was required to perceive an improvement in symptom intensity. While noting that the MCID would likely vary depending on the clinical context and patient population and robust validation would require consistent and reproducible data across multiple studies and patient populations, the ESC considered that a mean change of 1.0 point may be a reasonable estimate of the MCID.
- 6.20 With regards to uSFR, the ESC noted that Moller et al 2022¹⁵ reported a mean uSFR of 0.808 g/min (range: 0.165–2.442) in a healthy group of people (n = 130) and therefore considered the mean (SD) baseline uSFR reported in the SIAXI trial was low in comparison (0.40 [0.26] g/min). The ESC noted that the nominated MCID for uSFR represents only 20–30% of the likely SD for uSFR. The ESC considered that this was a small percentage and raised uncertainties related to the significance of this value compared to the range and likely distribution of the uSFR. The ESC considered further information related to the uSFR data distribution at baseline would be useful.
- 6.21 The SIAXI trial was not powered to detect a statistically significant difference in DSFS at Week 4. The proposed clinical algorithm indicated that patients could continue treatment if the DSFS score improved by ≥ 1 point. DSFS was the key outcome measure included in the economic model for adults, as it was used to define the health states in the model and transition probabilities (see paragraph 6.81).

¹⁴ Mercadante S, Adile C, Lanzetta G, Mystakidou K, Maltoni M, Guilherme Soares L, De Santis S, Ferrera P, Valenti M, Rosati M, Rossi R, Cortegiani A, Masedu F, Marinangeli F, Aielli F. Personalized Symptom Goals and Patient Global Impression on Clinical Changes in Advanced Cancer Patients. *Oncologist*. 2019 Feb;24(2):239-246. doi: 10.1634/theoncologist.2017-0668. Epub 2018 May 16. PMID: 29769382; PMCID: PMC6369942.

¹⁵ Møller PR, Kaersgaard ML, Grydehøj J, Ovesen T. Normal salivary production using a swab method in clinical settings. *Clin Otolaryngol*. 2022 Sep;47(5):583-588. doi: 10.1111/coa.13953. Epub 2022 Jul 12. PMID: 35724318; PMCID: PMC9544226.

- 6.22 The submission only presented EuroQol 5-Dimension 3-Level visual analogue scale (EQ-5D-3L VAS) results i.e., not the results for the EQ-5D-3L dimensions, which were used in the economic evaluation for adults.

Children and adolescents

- 6.23 The SIPEXI trial included children and adolescents (2 to 17 years old) with a neurologic disorder (e.g., cerebral palsy (64.7%) or TBI (3.9%)) or intellectual disability (31.4%) associated with chronic sialorrhea for ≥ 3 months before screening. A modified teacher's drooling scale (mTDS score of ≥ 6 ("severe drooling to the extent that clothing becomes damp occasionally"), rated by the investigator, was also required.
- 6.24 The co-primary outcomes in the SIPEXI trial were uSFR and GICS at Week 4. The secondary outcomes included GICS at Week 8 and 12, mTDS and safety. These outcomes were used for the clinical claim and deemed relevant for the economic analysis. The SIPEXI trial did not collect DSFS data; instead, it collected mTDS and defined severe drooling as mTDS ≥ 6 .
- 6.25 There were some differences between patients in the incobotulinumtoxinA and placebo arms in terms of concomitant disease and prior medications, but these differences were considered unlikely to bias the results.
- 6.26 The sample size for the children aged 2–5 years was small (n=36, 14% of the intention to treat [ITT] population), no placebo control arm was included for ethical reasons, and the uSFR was not assessed because the procedure was not considered suitable for small children.
- 6.27 Similar to the SIAXI trial, the submission stated that there were no established or validated MCIDs for sialorrhea treatment in any of the outcomes measured in the SIPEXI trial. The submission proposed the same MCIDs for uSFR and GICS that was proposed for the SIPEXI trial: uSFR = 0.05 g/min, GICS score = 1.0 point. As stated above (paragraph 6.18), the protocols that described the chosen MCIDs, were not provided with the submission and therefore their methodology and reliability could not be validated during the evaluation. The SIPEXI trial protocol that was provided with the PSCR stated that for the 6–17 years age group, the trial was powered to have a 95% probability of detecting a difference in mean change in uSFR at Week 4 between the incobotulinumtoxinA and placebo arms of 0.05 ± 0.22 (SD) mL/min, and a difference in mean GICS scores at Week 4 of 1.0 ± 1.93 (SD). The ESC considered that the nominated MCID for the GICS was likely reasonable, however considered the MCID nominated for uSFR was too small compared to the likely data distribution (see paragraph 6.19).
- 6.28 The SIPEXI trial did not collect quality-of-life data. Utility values for the economic model for children and adolescents were based on the EQ-5D-3L data collected in the SIAXI trial.

Comparative effectiveness

Adults

6.29 Table 4 presents the SIAXI trial (main phase) results for continuous co-primary and secondary outcomes.

Table 4: Results of co-primary and secondary outcomes in the main phase of the SIAXI trial: continuous data [with outcome presented as least-squared mean change from baseline]

Week	ICBT-A 100U (N=74)	PBO (N=36)	LS mean difference vs PBO	ICBT-A 100U (N=74)	PBO (N=36)	LS mean difference vs PBO
Co-primary outcomes (LS-mean difference, 95% CI)						
	uSFR			GICS		
4	-0.13, (-0.18; -0.08)	-0.04 (-0.11; 0.03)	-0.09 (-0.15; -0.03) P=0.004	1.25 (0.97; 1.53)	0.67 (0.30; 1.04)	0.58 (0.22; 0.94); P=0.002
Secondary Outcomes (LS-mean difference, 95% CI)						
	uSFR			GICS		
1	NR			0.96 (0.70; 1.23)	0.67 (0.34; 1.00)	0.29 (-0.02; 0.60) P=0.065
2				1.11 (0.84; 1.38)	0.83 (0.47; 1.18)	0.29 (-0.05; 0.62) P=0.096
8	-0.13 (-0.19; -0.08)	-0.02 (-0.08; 0.05)	-0.12 (-0.18; -0.06) P<0.001	1.30 (1.01; 1.59)	0.47 (0.09; 0.84)	0.84 (0.46; 1.21) P<0.001
12	-0.12 (-0.17; -0.07)	-0.03 (-0.09; 0.04)	-0.09 (-0.15; -0.03) P=0.004	1.21 (0.91; 1.51)	0.56 (0.17; 0.95)	0.65 (0.25; 1.04) P=0.001
16	-0.11 (-0.17; -0.06)	-0.01 (-0.08; 0.06)	-0.10 (-0.17; -0.04) P=0.002	0.93 (0.63; 1.23)	0.41 (0.02; 0.80)	0.52 (0.12; 0.92) P=0.011
Additional Secondary outcomes, (LS-mean difference^a, 95% CI)						
	DSFS			EQ-5D-3L VAS^b		
4	-1.66 (-2.12; -1.20)	-0.50 (-1.08; 0.09)	-1.17 (-1.71; -0.62) P<0.001	1.58 (13.29)	-2.20 (12.82)	NA
8	-1.97 (-2.44; -1.49)	-0.68 (-1.28; -0.08)	-1.29 (-1.86; -0.71) P<0.001	2.72 (14.01)	2.03 (15.82)	
12	-1.62 (-2.09; -1.16)	-1.00 (-1.59; -0.40)	-0.63 (-1.19; -0.06) P=0.030	3.65 (15.74)	-4.03 (17.89)	
16	-1.18 (-1.64; -0.73)	-0.75 (-1.33; -0.17)	-0.43 (-0.98; 0.11) P=0.116	1.26 (16.70)	0.44 (19.12)	

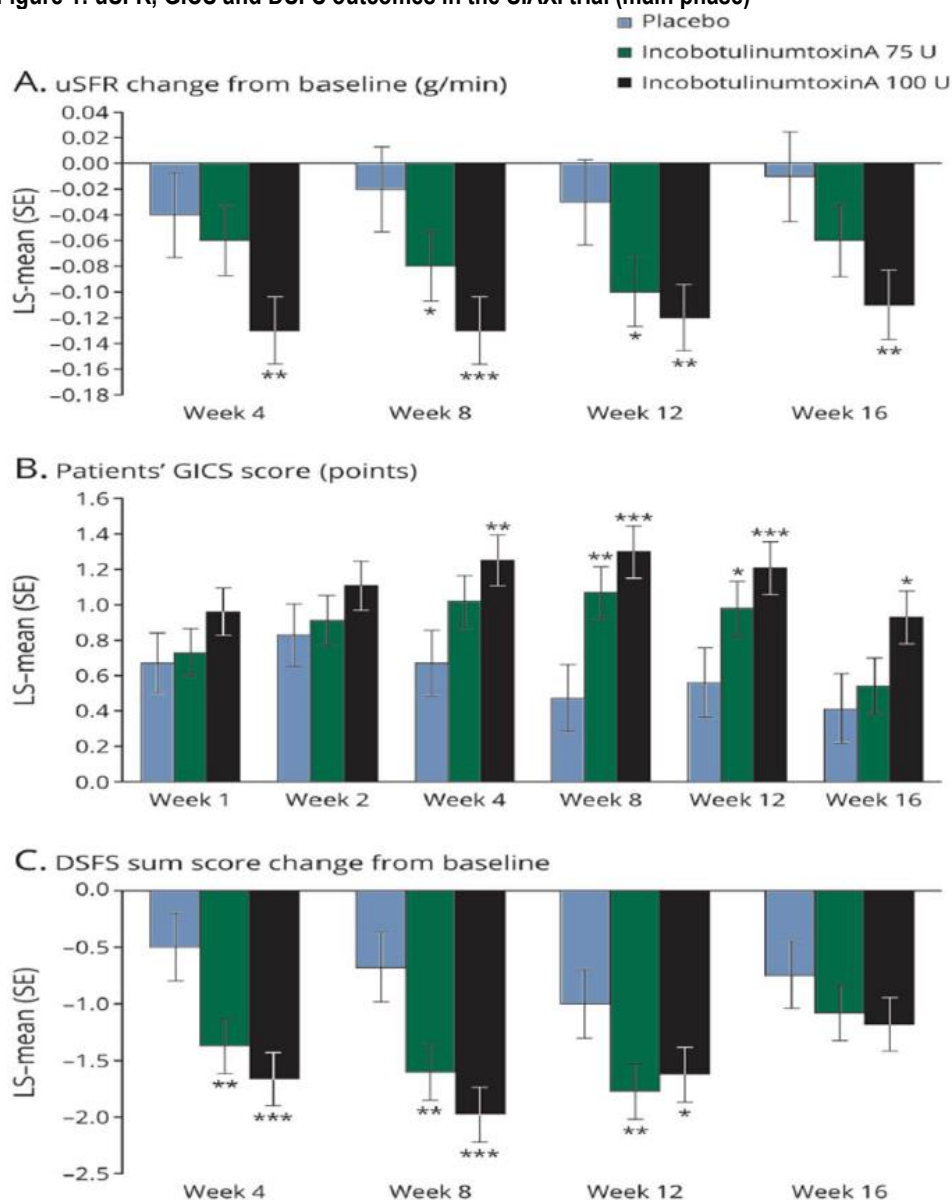
Source: Compiled during the evaluation based on Tables 2.5.1-2.5.7, pp51-56 of the submission; Table 2.5.9, p57 of the submission; pp148, 150, 154 & 156 of the SIAXI trial CSR.

CI = confidence interval; DSFS = drooling severity and frequency scale; EQ-5D-3L VAS= Euroqol-5 dimensional 3 levels visual analogue scale; GICS = Global Impression of Change Scale; ICBT-A = IncobotulinumtoxinA; LS = Least squared; NA = Not available; NR = Not reported; PBO = placebo; uSFR = unstimulated salivary flow rate; W= Week; 100U = 100 units.

^a Mean differences (SD) were presented for EQ-5D-3L VAS.

6.30 Figure 1 presents a diagrammatic representation of the changes in uSFR, GICS, and DSFS scores from baseline to Week 16.

Figure 1: uSFR, GICS and DSFS outcomes in the SIAXI trial (main phase)



Source: Figure 2.5.1, p55 of the submission.

DSFS = drooling severity and frequency scale; GICS = Global Impression of Change Scale; LS-mean = least-squared mean; SE = standard error; uSFR = unstimulated salivary flow rate; 75U = 75 units; 100U = 100 units.

*p < 0.05, **p < 0.01, ***p ≤ 0.001, Analysis based on change from baseline vs placebo in panels A and C, and the rating at each posttreatment assessment vs placebo in panel B. Reduction in uSFR and DSFS indicated improvement.

6.31 IncobotulinumtoxinA 100U demonstrated a statistically significant decrease in uSFR compared with placebo at Week 4 (-0.09; 95% CI: -0.15, -0.03; p = 0.004). The difference was also greater than the submission's nominated MCID of 0.05 g/min at four weeks compared to placebo. The increase in GICS observed for incobotulinumtoxinA 100U compared with placebo at Week 4 (0.58; 95% CI: 0.22, 0.94; p = 0.002) was also statistically significant. It did not exceed the submission's nominated MCID of a 1.0 point increase.

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- 6.32 Change in LS-Mean difference from baseline in uSFR was also measured at Weeks 8, 12 and 16, with statistically significant between-group differences (i.e. $p < 0.05$) at these time points favouring the incobotulinumtoxinA 100U arm over the placebo arm. The clinical significance of the response was uncertain.
- 6.33 Change in GICS from baseline was also measured at Weeks 1, 2, 8, 12 and 16. The increase in GICS between the incobotulinumtoxinA and placebo arms did not exceed 1.0 point at any time point.
- 6.34 IncobotulinumtoxinA 100U demonstrated a statistically significant improvement (i.e. $p < 0.05$) in DSFS compared with placebo at weeks 4, 8 and 12. The evaluation considered the clinical significance of these differences was uncertain as the submission did not specify an MCID; however, the proposed treatment algorithm indicated that patients could continue treatment if the DSFS score improved by ≥ 1 point. Improvement in DSFS appears to wane from Week 8 to Week 16 (the difference in DSFS was not significant ($p = 0.116$) at Week 16).
- 6.35 Table 5 presents efficacy results for uSFR, GICS and DSFS in the open-label extension phase.

Table 5: Results of co-primary outcomes and secondary outcome (DSFS) in the open-label extension phase of the SIAXI trial

Outcomes and time points (Weeks)	n	Mean (SD)
uSFR, Mean change (SD) from trial baseline to		
Cycle 2		
Baseline	89	-0.08 (0.21)
4	88	-0.14 (0.27)
16	85	-0.14 (0.24)
Cycle 3		
Baseline	84	-0.14 (0.24)
4	84	-0.17 (0.25)
16	81	-0.17 (0.23)
Cycle 4		
Baseline	78	-0.15 (0.21)
4	77	-0.20 (0.22)
16	74	-0.16 (0.22)
End of study	80	-0.16 (0.22)
GICS^a, Mean (SD)		
Cycle 2		
1	89	0.98 (1.02)
2	88	1.28 (0.88)
4	88	1.18 (1.16)
8	88	1.27 (1.01)
16	85	0.62 (1.41)
Cycle 3		
4	84	1.13 (1.34)
8	84	1.23 (1.21)
16	81	0.86 (1.36)
Cycle 4		
4	77	1.40 (1.14)
8	77	1.40 (1.10)
16	74	1.36 (1.14)
End of study	80	1.31 (1.20)
DSFS sum score ^b , Mean change (SD) from trial baseline to		
Cycle 2	88	-2.34 (1.55)
Cycle 3	84	-2.64 (1.56)
Cycle 4	77	-3.04 (1.71)

Source: Compiled during the evaluation based on pp169-171, 174 of the SIAXI trial CSR.

DSFS = drooling severity and frequency scale; GICS = global impression of change scale; SD = standard deviation; uSFR = unstimulated salivary flow rate.

^a Only patient-reported GICS scores are presented in the table.

^b Week 4 results for all cycles.

6.36 Mean decreases, i.e., improvements, in uSFR in the incobotulinumtoxinA 100 U arm was observed from baseline to each post-baseline visit in the open-label extension phase. The mean change (SD) from baseline to Week 16 ranged between -0.14 (0.24) to 0.17 (0.23) in the incobotulinumtoxinA 100U arm.

- 6.37 During the open-label extension phase of the SIAXI trial, improvements in GICS scores (i.e. GICS \geq 1) were observed at all visits and a slight increase of improvements was observed over the course of the trial. The GICS results were highest at the week 4 and week 8 visits of each injection cycle and slightly waned thereafter.
- 6.38 The DSFS score decreased, i.e. improved, from study baseline to each week 4 visit of the individual injection cycles in the open-label extension phase.
- 6.39 None of the EQ-5D-3L VAS results were statistically significantly different at Weeks 4 to 16 from baseline.
- 6.40 The submission used DSFS score data from the SIAXI trial to inform the economic model. The submission also applied EQ-5D-3L data from the SIAXI trial.

Children and adolescents

- 6.41 Table 6 presents the results of the SIPEXI trial (main phase) for the continuous co-primary and secondary outcomes.

Table 6: Results of co-primary and secondary outcomes in the main phase of the SIPEXI trial: continuous data [with outcome presented as mean change from baseline]

Week	uSFR (6-17 years)			GICS (6-17 years)		
	ICBT-A (N=148)	Placebo (N=72)	LS mean difference vs PBO	ICBT-A (N=148)	Placebo (N=72)	LS mean difference vs PBO
Co-primary outcomes, Mean difference (95% CI)						
4	-0.14 (-0.16; -0.11)	-0.07 (-0.10; -0.04)	-0.06 (-0.10; -0.03) P=0.0012	0.91 (0.76; 1.06)	0.63 (0.43; 0.84)	0.28 (0.02; 0.53) P=0.0320
Secondary Outcomes, Mean difference (95% CI)						
8	-0.16 (-0.18; -0.13)	-0.07 (-0.10; -0.04)	-0.09 (-0.12; -0.05) P<0.0001	0.94 (0.81; 1.07)	0.54 (0.35; 0.73)	0.40 (0.17; 0.63) P=0.0008
12	-0.16 (-0.19; -0.14)	-0.06 (-0.10; -0.03)	-0.10 (-0.14; -0.06) P<0.0001	0.87 (0.73; 1.02)	0.47 (0.25; 0.69)	0.40 (0.14; 0.66) P=0.0026
16	-0.15 (-0.18; -0.12)	-0.08 (-0.11; -0.05)	-0.07 (-0.11; -0.03) P=0.0003	0.77 (0.63; 0.91)	0.38 (0.17; 0.58)	0.39 (0.15; 0.63) P=0.0018

Source: Compiled during the evaluation based on Tables 2.5.10-2.5.13,2.5.16-2.5.17, pp58-63 of the submission.

CI = confidence interval; DSFS = drooling severity and frequency scale; GICS = Global Impression of Change Scale; ICBT-A = IncobotulinumtoxinA; LS = Least squared; NR = Not reported; PBO = placebo; uSFR = unstimulated salivary flow rate; W= Week.

Bold indicates statistically significant results for the incobotulinumtoxinA 100U arm compared to the placebo arm.

- 6.42 IncobotulinumtoxinA demonstrated a statistically significant decrease in uSFR in the 6-17 years age group compared with placebo at Week 4 (-0.06; 95% CI: -0.10, -0.03; p = 0.002). The difference was greater than the submission's nominated MCID of 0.05 g/min at four weeks compared to placebo. The increase in GICS observed for incobotulinumtoxinA compared with placebo at Week 4 (0.28; 95% CI: 0.02, 0.53; p = 0.0320) was also statistically significant; however, it did not exceed the submission's nominated MCID of a 1.0 point increase.
- 6.43 The total proportion of participants whose functional change due to treatment was rated on the GICS by the carer to have at least +1 'minimally improved', i.e., participants defined as responders at Week 4, was higher in the incobotulinumtoxinA 100U arm (6-17 years age group, 70.9%) than in the placebo (6-17 years age group,

45.8%). The proportion of responders in the 2–5 years age group (no placebo control) increased over time: 74.3% (Week 4), 73.5% (Week 8), 79.4% (Week 12), and 88.2% (Week 16).

6.44 Table 7 presents the mean carer- and investigator-rated mTDS scores for both 2–5 years and 6-17 years age groups.

Table 7: Results of mTDS scores in the main phase of the SIPEXI trial

Week	Carer's mTDS ratings, mean difference (SD)			Investigator's mTDS ratings, mean difference (SD)		
	ICBT-A (N=148), 6-17 years	Placebo (N=72), 6-17 years	ICBT-A (N=35) (2–5 years)	ICBT-A (N=148), 6-17 years	Placebo (N=72), 6-17 years	ICBT-A (N=35) (2–5 years)
4	-1.5 (1.6)	-1.0 (1.4)	-2.0 (1.7)	-1.7 (1.7)	-1.1 (1.4)	-2.3 (1.8)
8	-1.7 (1.6)	-1.2 (1.5)	-2.3 (2.0)	-2.0 (1.6)	-1.1 (1.4)	-2.5 (2.1)
12	-1.7 (1.6)	-1.1 (1.4)	-2.4 (1.9)	-2.0 (1.7)	-1.2 (1.4)	-2.7 (2.1)
16	-1.5 (1.4)	-1.0 (1.4)	-2.0 (1.6)	-1.5 (1.4)	-1.1 (1.4)	-2.1 (1.8)

Source: Compiled during the evaluation based on Tables 2.5.14-2.5.15, pp61-62 of the submission.

ICBT-A = IncobotulinumtoxinA; mTDS = modified teachers drooling scale; SD = standard deviation

Bold indicates statistically significant results for the incobotulinumtoxinA 100U arm compared to the placebo arm.

6.45 The submission reported that in both carer and investigator ratings across either age group, the reduction in mTDS scores was highest in Weeks 8 and 12. The SIPEXI trial was not designed to demonstrate statistically significant improvements in mTDS, and there was no specified MCID.

6.46 Table 8 presents results for the co-primary outcomes and secondary outcome results for mTDS in the open-label extension phase of the SIPEXI trial. The submission stated that consistent improvements in uSFR and mTDS scores were observed during each treatment cycle over the extension phase and for the carer's GICS ratings.

Table 8: Results of co-primary and secondary outcome (mTDS) in the extension phase of the SIPEXI trial

Outcomes and time points (Weeks)	ICBT-A (MP=Placebo, 6-17 years)	ICBT-A (MP= ICBT-A, 6-17 years)	ICBT-A (MP=no placebo, 2-5 years)
uSFR, Mean (SD) change from trial baseline			
16	-0.07 (0.15)	-0.14 (0.22)	NA ^a
20	-0.17 (0.19)	-0.26 (0.23)	
32	-0.15 (0.22)	-0.19 (0.19)	
36	-0.25 (0.19)	-0.29 (0.21)	
48	-0.21 (0.18)	-0.23 (0.20)	
52	-0.28 (0.19)	-0.32 (0.21)	
60	-0.30 (0.20)	-0.32 (0.23)	
64	-0.26 (0.21)	-0.31 (0.22)	
GICS^b, Mean (SD)			
20	1.2 (1.0)	1.5 (0.9)	1.7 (0.8)
24	1.3 (0.9)	1.5 (0.8)	1.5 (0.9)
28	1.3 (0.8)	1.5 (0.9)	1.4 (1.0)
32	1.3 (0.9)	1.4 (0.9)	1.3 (1.0)
36	1.8 (0.8)	1.7 (0.9)	1.9 (0.6)
40	1.9 (0.8)	1.8 (0.9)	1.8 (0.7)
44	1.6 (0.9)	1.6 (0.9)	1.5 (0.9)
48	1.4 (1.0)	1.6 (1.0)	1.4 (0.9)
52	1.9 (0.9)	1.9 (1.0)	2.2 (0.8)
56	1.9 (0.9)	2.1 (0.9)	2.2 (0.9)
60	1.8 (0.9)	2.0 (1.0)	1.9 (1.0)
64	2.1 (0.9)	2.0 (1.1)	2.0 (1.1)
mTDS^c, Mean (SD) change from trial baseline			
16	-1.0 (1.4)	-1.5 (1.4)	-2.0 (1.5)
20	-2.5 (1.7)	-3.2 (1.7)	-3.7 (1.8)
24	-2.9 (1.6)	-3.2 (1.6)	-3.7 (1.8)
28	-2.9 (1.7)	-3.0 (1.7)	-3.3 (1.8)
32	-2.7 (1.8)	-2.4 (1.7)	-2.6 (2.0)
36	-3.8 (1.7)	-3.8 (1.7)	-4.3 (1.5)
40	-4.1 (1.7)	-3.9 (1.7)	-4.2 (1.5)
44	-3.6 (1.7)	-3.8 (1.7)	-3.8 (1.6)
48	-3.2 (1.7)	-3.0 (2.0)	-2.9 (1.9)
52	-4.2 (1.7)	-4.3 (1.7)	-4.8 (1.7)
56	-4.5 (1.8)	-4.5 (1.7)	-4.8 (1.6)
60	-4.3 (1.7)	-4.6 (1.9)	-4.6 (1.6)
64	-4.5 (1.9)	-4.6 (2.0)	-4.7 (1.9)

Source: Compiled during the evaluation based on 145-147 of the SIPEXI trial CSR.

GICS = global impression of change scale; ICBT-A = incobotulinumtoxinA; MP = main phase; mTDS = modified teacher's drooling scale; NA = Not available; SD = standard deviation; uSFR = unstimulated salivary flow rate

^a Not reported in 2-5 years age group due to ethical issues.

^b Carer's GICS ratings.

^c Carer's mTDS ratings.

6.47 uSFR was the only efficacy outcomes from the SIPEXI trial used in the economic model. The submission indirectly used uSFR in the SIPEXI trial to generate the DSFS scores based on the SIAXI trial for adults. For placebo patients it was assumed that the DSFS

scores in the placebo arm of the SIPEXI trial were the same as the DSFS scores in the placebo arm of the SIAXI trial (adults). A ratio based on the difference in percentage gain between uSFR and DSFS measures at each time point in Cycle 1 (weeks 4, 8, 12, and 16) in the SIAXI trial was applied to the uSFR percentage gain from the SIPEXI trial. This estimated DSFS percentage gain for Cycle 1 was then used to generate the DSFS scores for the incobotulinumtoxinA arm. The evaluation considered that this approach was uncertain as the children and adolescents had different characteristics and different conditions compared with the adults. Furthermore, no evidence was provided supporting the assumption that the percentage gain in uSFR was associated with the percentage gain in DSFS scores.

Comparative harms

Adults

6.48 Table 9 summarises the safety outcomes for the safety population in the SIAXI trial.

Table 9: Summary of key adverse events in the SIAXI trial (main trial phase)

Number, n (%) of participants with	ICBT-A 75U (N=74)	ICBT-A 100U (N=74)	Placebo (N=36)
Any TEAE	32 (43.2%)	34 (45.9%)	15 (41.7%)
Any TEAE related to treatment	7 (9.5%)	6 (8.1%)	3 (8.3%)
Any TEAESI	5 (6.8%)	5 (6.8%)	0
Any TEAESI related to treatment	3 (4.1%)	1 (1.4%)	0
Any TESAE	6 (8.1%)	9 (12.2%)	3 (8.3%)
Any TESAE related to treatment	0	0	0
Any TEAE leading to discontinuation	1 (1.4%)	1 (1.4%)	0
Any TEAE leading to discontinuation related to treatment	0	0	0
Any fatal TEAE	0	0	0
Any fatal TEAE related to treatment	0	0	0

Source: Table 2.5.18, pp66-67 of the submission.

ICBT-A = IncobotulinumtoxinA; n = number of participants reporting data; N = total participants in group; TEAE = Treatment-emergent adverse event; TEAESI = treatment-emergent adverse event of special interest; TESAE = treatment-emergent serious adverse event.

6.49 The frequency of treatment-emergent adverse events (TEAEs) (45.9% with incobotulinumtoxinA 100U vs 41.7% with placebo) and treatment-related TEAEs (8.1% with incobotulinumtoxinA 100U vs 8.3% with placebo) was similar between the treatment arms in the main phase of the SIAXI trial. The submission stated that treatment related TEAEs were of mild or moderate intensity.

6.50 During the main trial phase of the SIAXI trial, the most frequently reported TEAEs among the incobotulinumtoxinA 100U arm participants included tooth extraction (5.4%), dry mouth, diarrhoea, and hypertension (4.1% each). Dry mouth (5.4%) and dysphagia (4.1%) were also reported in the incobotulinumtoxinA 75U arm. No treatment-emergent serious adverse events (TESAEs) in either arm were considered to be related to treatment.

6.51 The most frequently reported TEAEs among the incobotulinumtoxinA 100U arm during the extension phase of the SIAXI trial included dry mouth (11.2%), nasopharyngitis (6.7%), and fall (5.6%).

- 6.52 The overall discontinuation rate due to TEAEs during the main phase of the SIAXI trial was low (1.4%).
- 6.53 The SIAXI trial was too short to determine long-term adverse events (AEs) relating to incobotulinumtoxinA 100U.
- 6.54 The submission did not consider costs or disutilities related to AEs in the economic evaluation.

Children and adolescents

- 6.55 Table 10 summarises the safety outcomes for the safety population in the main phase of the SIPEXI trial.

Table 10: Summary of key adverse events in the SIPEXI trial (main trial phase)

	ICBT-A (N=148), 6-17 years	Placebo (N=72), 6-17 years	ICBT-A (N=35), 2-5 years
Any TEAE	27 (18.2%)	11 (15.3%)	5 (14.3%)
Any TEAESI	1 (0.7%)	0	0
Any TEAESI related to treatment	1 (0.7%)	0	0
Any TESAE	0	1 (1.4%)	1 (2.9%)
Any TESAE related to treatment	0	0	0
Any TEAE related to treatment	2 (1.4%)	0	1 (2.9%)
Any TEAE leading to discontinuation	1 (0.7%)	1 (1.4%)	1 (2.9%)
Any TEAE leading to discontinuation related to treatment	0	0	0
Any fatal TEAE	0	0	0
Any fatal TEAE related to treatment	0	0	0

Source: Table 2.5.20, p70 of the submission.

ICBT-A = IncobotulinumtoxinA; n = number of participants reporting data; N = total participants in group; TEAE = Treatment-emergent adverse event; TEASI = treatment-emergent adverse event of special interest; TESAE = treatment-emergent serious adverse event.

- 6.56 The proportion of participants who experienced at least one TEAE was marginally higher in the incobotulinumtoxinA arm (6–17 years age group, 18.2%) compared to the placebo arm (6–17 years age group, 15.3%) and the 2–5 years age group (14.3%). The incidence of TEAEs and TESAEs related to treatment was low across all groups.
- 6.57 During the main trial phase of the SIPEXI trial, the most frequently reported TEAEs among the incobotulinumtoxinA participants aged 2–5 years included nasopharyngitis (5.7%), and among participants aged 6–17 years included pharyngitis (3.4%) and nasopharyngitis (2.0%). No AEs related to general anaesthesia were reported.
- 6.58 The overall discontinuation rate due to TEAEs during the main phase of the SIPEXI trial was low (0.7% in the 6–17 years age group, 2.9% in the 2–5 years age group).
- 6.59 The most frequently reported TEAEs among the incobotulinumtoxinA arm during the extension phase of the SIPEXI trial was nasopharyngitis (6.1%) in the 6–17 years age group and respiratory tract infection viral (12.1%) in the 2–5 years age group. During the entire period of the SIPEXI trial, 5 participants in the 6–17 years age group experienced dysphagia (one (0.7%) in the main phase and 4 (1.9%) in the extension phase), potentially indicating toxin spread related to incobotulinumtoxinA. However, dysphagia in all participants was assessed to be of mild to moderate intensity. During the entire study period, dry mouth was reported in 2 subjects (0.8%).

- 6.60 During the extension phase, 2 patients (1.4%) discontinued in the second injection cycle, and a further 2 patients (1.4%) discontinued in the third injection cycle.
- 6.61 Only the TEAEs of dysphagia, saliva altered, and choking which led to the discontinuation of one patient, were considered by the investigator as being related to treatment.
- 6.62 The SIPEXI trial was too short to determine long-term AEs relating to incobotulinumtoxinA. There may also be AEs that develop following repeated use of general anaesthesia in children.
- 6.63 The submission did not consider costs or disutilities related to AEs in the economic evaluation.

Benefits/harms

- 6.64 A summary of the comparative benefits and harms for incobotulinumtoxinA versus placebo is presented in Table 11.

Table 11: Summary of comparative benefits and harms for incobotulinumtoxinA and placebo (main period)

Trial	ICBT-A ^a			PBO			LS-Mean difference*: ICBT-A vs PBO (95% CI), P-value
	N	Mean Δ baseline	SD	N	Mean Δ baseline	SD	
Benefits							
uSFR^b at Week 4, Full analysis set analysis							
SIAXI	74	-0.13	0.21	36	-0.04	0.21	-0.09 (-0.15, -0.03) P=0.004
SIPEXI (6-17 years)	148	-0.14	0.17	72	-0.07	0.15	-0.06 (-0.10, -0.03) P=0.012
GICS^b at Week 4, Full analysis set analysis							
SIAXI	74	1.25	0.14	36	0.67	0.19	0.58 (0.22, 0.94) P=0.002
SIPEXI (6-17 years)	148	0.91	0.08	72	0.63	0.10	0.28 (0.02, 0.53) P=0.0320
DSFS^b at Week 4, Full analysis set analysis							
SIAXI	74	-1.66	0.234	36	-0.50	0.296	1.17 (-1.71, -0.62) P<0.001
Carer's mTDS at Week 4, Full analysis set analysis							
SIPEXI (6-17 years)	74	-1.5	1.6	36	-1.0	1.4	NR
Harms							
	ICBT-A		PBO n/N	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
					ICBT-A	PBO	
Any TEAE							
SIAXI	34/74		15/36	NA	45.9	41.7	4.2 (-15, 24)
SIPEXI (6-17 years)	27/148		11/72	NA	18.2	15.3	2.9 (-7, 13)
Nervous system disorders							
SIAXI	7/74		1/36	NA	9.5	2.8	6.7 (-2, 15)
Surgical and medical procedures							
SIAXI	6/74		0/36	NA	8.1	0.0	8.1 (2, 14)
Tooth extraction							
SIAXI	4/74		0/36	NA	5.4	0.0	5.4 (0, 11)
Dry mouth							
SIAXI	3/74		0/36	NA	4.1	0.0	4.1 (-0.4, 9)
Respiratory, thoracic and mediastinal disorders							
SIAXI	3/74		0/36	NA	4.1	0.0	4.1 (-0.4, 9)
Eye disorders							
SIAXI	3/74		0/36	NA	4.1	0.0	4.1 (-0.4, 9)

Source: Tables 2.5.1-2.5.7, pp51-56 of the submission; Tables 2.5.10-2.5.13, 2.5.16-2.5.17, pp58-63 of the submission; Tables 2.5.14-2.5.15, pp61-62 of the submission; Table 2.5.18, pp66-67 of the submission; Table 2.5.19, pp67-68 of the submission; Tables 2.5.20, p70 of the submission; p190 of the SIAXI trial CSR.

CI = confidence interval; GICS = Global impression of change scale; DSFS = Drooling severity and frequency scale; ICBT-A = IncobotulinumtoxinA; LS = Least-squared; mTDS = modified teacher's drooling scale; NA = Not available; NR = Not reported; PBO = placebo; RD = risk difference; RR = risk ratio; TEAE = Treat-emergent adverse event; uSFR = unstimulated salivary flow rate.

* Mean duration of follow-up for both trials: Main trial phase: 16±2 weeks; Open-label extension phase: 3 x 16±2 weeks cycles.

^a IncobotulinumtoxinA 100U in the SIAXI trial; IncobotulinumtoxinA in the SIPEXI trial.

^b Least-squared mean differences presented for this outcome.

6.65 On the basis of direct evidence presented by the submission, the comparison of incobotulinumtoxinA and placebo resulted in:

- Approximately 0.09 g/min improvement in uSFR from baseline to Week 4 among adults (an improvement of 0.05 g/min improvement was considered by the

submission to be clinically significant). At Week 16, the improvement was -0.10 g/min.

- Approximately 0.58 point improvement in GICS score from baseline to Week 4 among adults (ranges from -3 (very much worse) to +3 (very much improved); an improvement of ≥ 1.0 in the GICS was considered a responder by the submission). At Week 16, the improvement was 0.52.
- Approximately 1.17 point improvement in DSFS score from baseline to Week 4 among adults (ranges from 2 (best) to 9 (worst)). At Week 16, the improvement was 0.43.
- Approximately 0.06 g/min improvement in uSFR from baseline to Week 4 among children and adolescents (6–17 years) (an improvement of 0.05 g/min improvement was considered by the submission to be clinically significant). At Week 16, the improvement was -0.07 g/min.
- Approximately 0.28 point improvement in GICS score from baseline to Week 4 among children and adolescents (6–17 years) (ranges from -3 (very much worse) to +3 (very much improved); an improvement of ≥ 1.0 in the GICS was considered a responder by the submission). At Week 16, the improvement was 0.39.

6.66 It was not possible to determine if these improvements were clinically meaningful.

6.67 On the basis of direct evidence presented by the submission, for every 100 patients treated with incobotulinumtoxinA in comparison with placebo over the 16 weeks period:

- Approximately 4 additional adult patients would experience a treatment-emergent adverse event.
- Approximately 3 additional patients aged 6-17 years old would experience a treatment-emergent adverse event.
- Approximately 7 additional adult patients would experience nervous system disorders.
- Approximately 8 additional adult patients would experience surgical and medical procedures-related complications.
- Approximately 5 additional adult patients would experience tooth extraction.
- Approximately 4 additional adult patients would each experience dry mouth, respiratory, thoracic and mediastinal disorders, and eye disorders.

Clinical claim

6.68 The submission described incobotulinumtoxinA 100U as superior in terms of effectiveness compared to SoC (placebo) in adults and in children and adolescents.

6.69 The ESC noted that the claim of superior efficacy compared to SoC (placebo) in adults was associated with the following uncertainties:

- The submission proposed the following MCIDs: uSFR = 0.05 g/min, GICS score = 1.0 point. An MCID for DSFS was not available or proposed by the submission. The decrease in uSFR between the incobotulinumtoxinA arm and the placebo arms was greater than 0.05 g/min at Week 4; however, the ESC considered the clinical significance of this result was uncertain, as 0.05 g/min represented a small change in the context of the total uSFR distribution (see paragraph 6.19). The mean difference in GICS scores between the incobotulinumtoxinA and placebo arms did not exceed 1.0 point.
- The use of DSFS as eligibility criteria to initiate and continue incobotulinumtoxinA has several issues. The ESC considered that the lack of psychometric and statistical/clinical validation was the primary concern related to DSFS (see paragraph 3.8).
- The short trial duration of 16 weeks was not adequate to capture long-term outcomes, especially quality of life. Additionally, there is potential for the treatment effect of incobotulinumtoxinA to wane over time after repeated injections.
- The SIAXI trial included only 3 participants with TBI; therefore, the efficacy and safety results for these patients were uncertain.

6.70 The ESC noted that the claim of superior efficacy compared to SoC (placebo) in children and adolescents was associated with a number of uncertainties:

- The submission proposed the following MCIDs: uSFR = 0.05 g/min, GICS score = 1.0 point. Although the decrease in uSFR between the incobotulinumtoxinA arm and the placebo arms was greater than 0.05 g/min at Week 4, the clinical significance of this result was uncertain. The mean difference in GICS scores between the incobotulinumtoxinA and placebo arms did not exceed 1.0 point.
- The SIPEXI trial did not collect DSFS or quality of life data. The PSCR argued that the mTDS collected in the SIPEXI trial and the DSFS measure the same frequency and severity factors and are strongly correlated (correlation coefficient = 0.88)¹⁶.
- The main phase of the trial was 16 weeks, which may not be adequate to capture long-term outcomes, especially quality of life. Additionally, there is potential for the treatment effect of incobotulinumtoxinA to wane over time after repeated injections.
- The SIPEXI trial included only 10 participants with TBI (6-17 years age group: 9 in the incobotulinumtoxinA arm, one in the placebo arm, and 9 in the 2–5 years age

¹⁶ Perinelli, Martina Giorgia, et al. "Comparing subjective scales for rating drooling: a pilot, bicentric study." *Int J Neurorehabil* 9 (2022): 8.

group: none), therefore, the efficacy and safety results for these patients were uncertain.

- 6.71 The PSCR argued that while the pivotal trials measured a 16-week cycle of incobotulinumtoxinA efficacy and safety, the open-label extension followed patients for an additional 3 cycles (total weeks: 64) and demonstrated that benefit was maintained.
- 6.72 The ESC noted that incobotulinumtoxinA 100U arm demonstrated statistically significant improvements compared to placebo in the co-primary outcomes (uSFR and GICS) from baseline to Week 4 in both the SIAXI trial (adults) and the SIPEXI trial (children and adolescents). The ESC also noted that the mean differences for both outcomes from baseline to Week 4 in both trials were statistically significant. Therefore, while noting the uncertainties related to the clinical data and the nominated MCIDs, the ESC considered that the clinical claim of superior efficacy compared with SoC (placebo) was likely supported by the clinical data.
- 6.73 The submission described incobotulinumtoxinA as inferior in terms of safety compared to SoC (placebo) in both the adult and children and adolescent populations.
- 6.74 The therapeutic conclusions regarding safety for both adults and children and adolescents were adequately supported by the evidence. However, the trials were too short to determine long-term AEs relating to incobotulinumtoxinA. There may also be AEs that develop following repeated use of general anaesthesia in children.
- 6.75 The PBAC considered that the claim of superior comparative effectiveness was reasonable. However, considered the clinical significance of the observed benefit was uncertain.
- 6.76 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

- 6.77 The submission presented a stepped economic evaluation based on direct randomised trials (the SIAXI and SIPEXI trials) that compared incobotulinumtoxinA with SoC. Two models were presented:
- The adult population as included in the SIAXI trial – with chronic sialorrhea due to Parkinson's disease, atypical parkinsonism, stroke, or TBI.
 - The children and adolescents' population as included in the SIPEXI trial – chronic sialorrhea associated with neurologic disorders (e.g., cerebral palsy, TBI) or intellectual disability.
- 6.78 Both adult, children and adolescent models were the same and based on the model structure from Makino et al. (2020).
- 6.79 The type of economic evaluation presented was a cost-utility analysis, which was appropriate given the available evidence and claims of superiority. The stepped

analysis was not comprehensive, and additional stepped analyses were conducted during the evaluation.

6.80 Table 12 presents a summary of the economic models (adult and children and adolescent populations).

Table 12: Summary of model structure, key inputs and rationale

Component	Description
Type of analysis	Cost-utility analysis. This was appropriate given the claim of superior effectiveness.
Treatment	Treatment arm: incobotulinumtoxinA every 16 weeks Comparator arm: SoC
Outcomes	QALYs gained. No mortality gain was modelled, and so there would be no impact on life years gained.
Time horizon	5 years in both models. The time horizon in the model (5 years) was long compared to the duration of follow-up in the open-label extension of the SIAXI trial (median 64 weeks).
Methods used to generate results	Markov state transition model.
Health states	Mild/resolved sialorrhea (DSFS 2-3), moderate sialorrhea (DSFS 4-6), severe sialorrhea (DSFS 7-9), treatment discontinuation, dead. Patients transitioned between these health states reflecting improvement/worsening of their sialorrhea severity over time. The health states reflected those of Makino et al. (2020). The impact of using DSFS 7-9 to reflect severe sialorrhea and DSFS 4-6 for moderate sialorrhea, and thus the ICER, was unclear.
Cycle length	16 weeks. This reflected the re-injection interval in SIAXI and SIPEXI trial.
Transition probabilities	<p>Adults: Post hoc analysis of DSFS data from the SIAXI trial and extension phase to estimate the transition probabilities that informed the movement of the modelled cohort across three severity-based health states (mild/resolved sialorrhea (DSFS 2-3), moderate sialorrhea (DSFS 4-6), severe sialorrhea (DSFS 7-9)). The use of the DSFS to determine transition probabilities has several issues (see paragraph 3.8) which increased the uncertainty in the results. Additionally, the change in DSFS scores was a secondary outcome of the SIAXI trial.</p> <p>Children and adolescents: As per the adult model, with imputed DSFS scores based on uSFR from the SIPEXI trial. The evaluation considered that this approach was uncertain as the children and adolescent population had different characteristics and different conditions compared with the adults. Furthermore, no evidence was provided supporting the assumption that the percentage gain in uSFR was associated with the percentage gain in DSFS scores (e.g. scatter plot or regression).</p> <p>Extrapolation: Assumed no further transitions between health states after Cycle 4 (incobotulinumtoxinA) or Cycle 1 (SoC) as long as the patient remained on treatment. This approach assumed that treatment efficacy did not wane over time after repeated injections. The ESC considered that this was likely not reasonable due to the lack of data beyond 64 weeks.</p> <p>Discontinuation of incobotulinumtoxinA, adults: 2.7% in Cycle 1 based on the SIAXI trial and 3.1% from Cycle 2 and onwards based on the SIAXI trial extension phase.</p> <p>Discontinuation of SoC, adults: 11% in Cycle 1 based on the SIAXI trial. Discontinuation for Cycle 2 and onwards was assumed to be the same as Cycle 1. The ESC considered it is generally not possible to discontinue SoC, as SoC was assumed to consist of non-pharmacological interventions, such as using bibs or other clothing to wipe of saliva and other physical therapy such as posture adjustment, oral motor exercises. In this case, surgery or radiotherapy may be considered as a later line of therapy. However, the cost/effect of later line therapy options were not considered as part of the economic model.</p> <p>Discontinuation, children and adolescents: As per adults. This was uncertain given the 2 populations had different characteristics and conditions in the trials. It would have been more appropriate if the SIPEXI trial data was used to inform the discontinuation rate in the children and adolescent model.</p> <p>The sialorrhea severity for patients discontinuing treatment was assumed to revert to the mean severity observed at baseline.</p>

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Component	Description
	Mortality: ABS life tables. No disease-specific mortality rate was applied to the model. s approach underestimated life-threatening conditions and infections associated with sialorrhea.
Utilities	<p>Weighted average of the EQ-5D scores based on the SIAXI trial data for each of the DSFS-based health states. The model assumed that the baseline utility value (0.59) was the utility for patients who discontinued treatment. In general, it was reasonable to predict the impact of incobotulinumtoxinA on quality of life using the DSFS score (Thomas-Stonell and Greenberg 1988).</p> <p>Severe: 0.55 Moderate: 0.64 Mild/resolved: 0.74. Discontinued: 0.59</p> <p>The submission assumed the same utility value for children and adolescents as for adults. This was uncertain given the 2 populations had different characteristics and conditions in the trials.</p> <p>No adverse events were included in the model. This assumption was inconsistent with the clinical claim of inferior safety.</p>
Costs	<p>Adults, children and adolescents (incobotulinumtoxinA arm only) (severe, moderate, and mild/resolved health states) incurred the costs of incobotulinumtoxinA (\$, requested DPMQ 100-unit vial), consultation (MBS item 116), injection (MBS item 18374), and ultrasound fees (MBS item 55848) (55% of adults and all children and adolescents).</p> <p>Adults, children and adolescents (incobotulinumtoxinA arm and SoC arm) also incurred allied healthcare services (\$70.95, MBS item 10970) (such as speech pathology, physiotherapy or occupational therapy).</p> <ul style="list-style-type: none"> - Patients in severe state incurred 2 allied health services. - Patients in moderate state incurred 1 allied health service. - Patient in mild/resolved state incurred no allied health services. - Patients discontinued treatment incurred 1 allied health service. <p>No costs associated with AEs were applied. Anaesthesia costs were not included for children and adolescents which did not align with the SIPEXI trial, where general and local anaesthesia was offered to all children.</p>
Software package	Microsoft Excel.

Source: Table 3.1.1, p79 of the submission.

ABS = Australian Bureau of Statistics; EQ-5D = EuroQol 5-dimension; ICER = incremental cost effectiveness ratio; DSFS = Drooling Severity and Frequency Scale; QALY = quality adjusted life years.; uSFR = unstimulated salivary flow rate; SoC: Standard of Care

^a NICE (2019) Xeomin (botulinum neurotoxin type A) for treating chronic sialorrhea, technology appraisal guidance, published: 9 October 2019. [www.nice.org.uk/guidance.ta605](http://www.nice.org.uk/guidance/ta605)

6.81 The submission conducted a post hoc analysis of DSFS data to estimate the transition probabilities that informed the movement of the modelled cohort across 3 severity-based health states (mild/resolved sialorrhea (DSFS 2-3), moderate sialorrhea (DSFS 4-6), severe sialorrhea (DSFS 7-9)). The main phase of the SIAXI and SIPEXI trials was 16 weeks (1 cycle), followed by an open label extension phase for an additional 48 weeks (64 weeks and 4 cycles in total) for the treatment arms. DSFS was assessed in Week 4 of each cycle and this data were utilised to produce the transition matrix of each cycle. For the adult model, the DSFS data were available for the first 64 weeks (4 cycles) for the treatment arm and 16 weeks (1 cycle) for the SoC arm. Extrapolation of the health state transition probabilities was conducted on a last observation-carried forward (LOCF) basis; therefore, no further transitions among these health states occur after these time points in the model if patients remained on treatment. Patients could discontinue both incobotulinumtoxinA and placebo in the subsequent modelled cycles

- and move into the discontinued health state. For the children and adolescent model, the submission imputed DSFS scores, then followed the same method as the adult model to estimate the transition probabilities and movement among the health states.
- 6.82 The submission argued that the SIAXI trial showed that participants continued to improve in terms of DSFS score over time, and that if this trend were to be sustained, the extrapolation approach would have biased against incobotulinumtoxinA. This approach assumed that treatment efficacy did not wane. The ESC considered this was likely not reasonable, noting a lack of data beyond 64 weeks.
- 6.83 The submission applied a time horizon of 5 years in both models. The time horizon in the model was long compared to the duration of open-label extension of the SIAXI trial and SIPEXI trials (incobotulinumtoxinA arm = 64 weeks, placebo arm = 16 weeks). The PSCR argued that a 5-year time horizon was required to capture the full costs and outcomes of treatment. The PSCR stated that if patients demonstrate tolerance to treatment and continue to derive a sustained clinical benefit, then they are expected to continue therapy on a long-term basis and therefore, a time horizon longer than the clinical trial follow up was required. In the context of the assumption that treatment effect is maintained over the time horizon and in view of the lack of trial data beyond 64 weeks, the ESC considered a time horizon of 2 years would be more appropriate. The pre-PBAC Response maintained that a 5-year time horizon was more appropriate due to the chronic nature of the condition; however, also considered that the ICER remained cost-effective with a two-year time horizon applied to the model \$35,000 to < \$45,000/QALY gained in the adult model (base case = \$25,000 to < \$35,000/QALY) and \$35,000 to < \$45,000/QALY gained in the children and adolescent model (base case = \$35,000 to < \$45,000/QALY)).
- 6.84 For the adult population, the submission estimated the transition probabilities from severe to moderate or mild DSFS health state based on the DSFS results in the SIAXI trial population (100U arm) and the extension phase. The evaluation considered that the use of the DSFS to determine response, and thus transition probabilities, had several issues (see paragraph 3.8).
- 6.85 For children and adolescents, the submission imputed DSFS scores in the incobotulinumtoxinA arm using the SIAXI and SIPEXI trials (see paragraph 6.47). This approach increased uncertainty in the results compared to directly collecting the DSFS scores during the SIPEXI trial, because the children and adolescents had different characteristics and different conditions compared with the adults. Furthermore, no evidence was provided supporting the assumption that the percentage gain in uSFR was associated with the percentage gain in DSFS scores. In particular, no scatter plot or regression was provided to support this assumption. The PCSR represented the correlation between uSFR and DSFS scores calculated in the submission. The PSCR also

considered that a systematic review (Sforza et al. 2022)¹⁷ supported that the relationship between uSFR and DSFS in adults was equivalent to that between uSFR and DSFS in children. This study reported DSFS scores correlated with quantitative measures of drooling as measured by bib count and bib weight; however, it did not analyse the correlation between the DSFS scores and mTDS, which was the scoring system set up to measure drooling severity in children and adolescents in the SIPEXI trial.

- 6.86 The submission assumed the same placebo DSFS scores for children and adolescents as for adults (see paragraph 6.47). Consequently, the transition probabilities in the SoC arm were the same as those for the adult transition probabilities. This was uncertain given the different patient populations. The submission could have conducted a linear regression to impute DSFS from uSFR, which could then be applied to the SoC arm of the SIPEXI trial to impute the DSFS scores.
- 6.87 For the adult model, the utility value of each health state was estimated based on the SIAXI trial individual patient data with Australian preference weights applied. The SIAXI trial collected patient EQ-5D-3L scores and DSFS scores then estimated the weighted average of the EQ-5D scores for each DSFS-based health state (severe = 0.55; moderate = 0.64; mild/resolved = 0.74; discontinued = 0.59).
- 6.88 The utility value in the discontinued health state (0.59) was higher than the severe health state (0.55), which was not plausible. Thus, a sensitivity analysis using 0.55 as the utility value for discontinued health state was conducted as a worst-case scenario during the evaluation. The results showed that the ICER decreased to \$15,000 to < \$25,000/QALY gained in the adult model (base case: \$25,000 to < \$35,000/QALY gained).
- 6.89 The submission assumed the same utility values for children and adolescents as for adults. This was uncertain, given the two populations had different characteristics and different conditions and there may also be AEs related to the repeated use of general anaesthesia in children.
- 6.90 No disutilities associated with AEs were applied to either model which was inconsistent with the clinical claim of inferior safety. The submission claimed that this had a minor impact on the model as only 8.1% of patients in the incobotulinumtoxinA 100U arm of the SIAXI trial experienced any TEAE related to treatment. The evaluation considered that the impact of adverse events on utilities would be captured in the average utility values collected during the trials. A sensitivity analysis using average utilities by treatment arm (average utility for incobotulinumtoxinA arm = 0.63; average utility for SoC arm = 0.59) was conducted during the evaluation and resulted in an ICER of \$35,000 to < \$45,000 per QALY for the adult model and \$35,000 to < \$45,000 per QALY for the children and adolescent model. The PSCR argued that the

¹⁷ Sforza, Elisabetta, et al. "Drooling outcome measures in paediatric disability: a systematic review." *European Journal of Pediatrics* 181.7 (2022): 2575-2592.

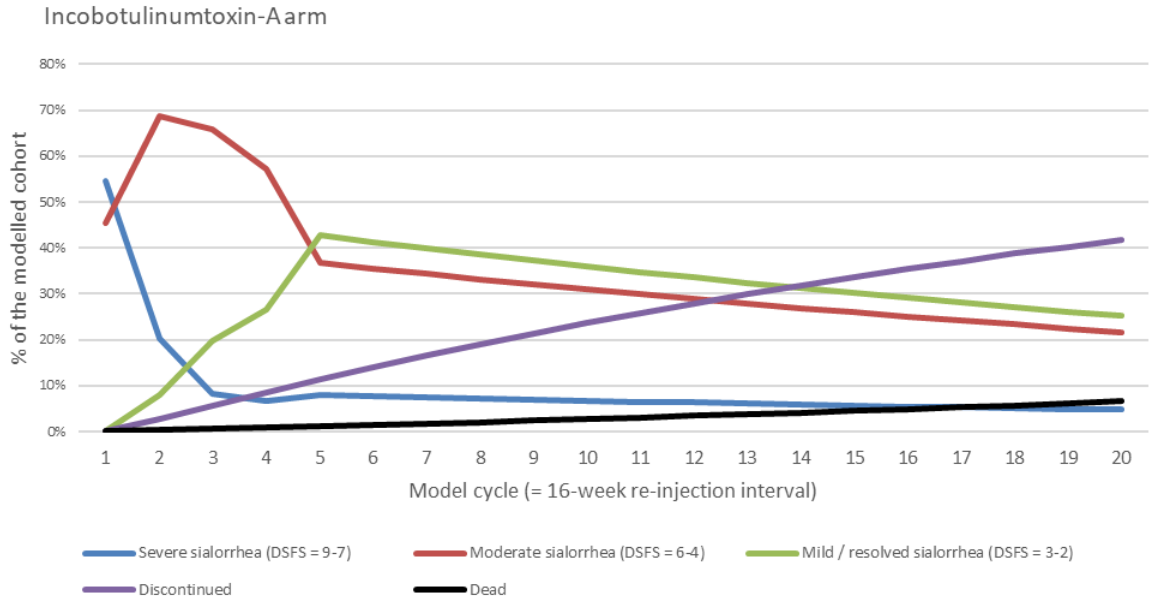
average utility values did not appropriately capture the relationship between quality-of-life and DSFS. The PSCR further argued that treatment-related AEs were low across all treatment arms in both trials and that the associated disutilities would be accounted for in the observed values applied in the base case in the models. The PSCR noted that if a patient's AEs were severe enough to discontinue treatment, the disutility of these patients would be captured in the utility used for discontinued patients.

- 6.91 Patients incurred the costs of incobotulinumtoxinA (\$) and consultation (MBS item 116), injection (MBS item 18374) and ultrasound fees (MBS item 55848; 55% of adults and all children and adolescents). The evaluation considered that the MBS item nominated in the submission for the injection fee (MBS item 18374 for the treatment of bilateral blepharospasm) was unlikely to capture the complexities and associated costs of treating this cohort of patients. The PSCR stated that the proposed MBS item for sialorrhea administration will align with that for bilateral blepharospasm (MBS items: 18372, 18374, fee: \$142.25) due to the number of injections used per indication. The ESC noted that in the SIAXI trial, each treatment was administered via four injections into the bilateral parotid and submandibular salivary glands, guided by ultrasound (60.8% 75 U; 55.4% 100 U) or anatomical landmarks (39.2% 75 U; 44.6% 100 U) at the discretion of the investigator. In the SIPEXI trial, ultrasound guidance was used for all injections in the safety evaluation set (SES) population (Clinical Study Report [CSR]). The ESC considered that for adult patients, injections were more commonly guided by anatomical landmarks than ultrasound in the Australian clinical setting. However, the ESC considered the proportion of children that would require ultrasound remained uncertain.
- 6.92 Additionally, the costs for adult patients could potentially differ to those for children and adolescents as in the SIPEXI trial, local and general anaesthesia, medication for analgesia, and analgo-sedation were offered to all patients unless contraindicated and in line with international guidelines on sedation in children. During the comparative trial period, analgesics and/or sedatives were used for more than 90% of patients in each arm and local anaesthetics were given to over 60% of patients. General anaesthetics were administered for 23.6% of the placebo group (6–17 years old), and for 11.4% and 25.7% of the incobotulinumtoxinA groups (2–5 years old, 6–17 years old, respectively). Further, some children, adolescents, and patients with Parkinson's disease and traumatic brain injury may require sedation, which is associated with a cost to the healthcare system. The economic model did not include the costs associated with local anaesthesia, sedation and/or analgesia or the fees associated with general anaesthesia, which the evaluation noted would be complex to estimate given that there are inpatient and outpatient MBS items and potential costs to the health care system from day admissions. The PSCR stated that as anaesthesia was not a requirement of the SIPEXI trial and that as expert opinion did not consider it necessary, it was not included. The pre-PBAC Response stated that injectable diazepam would be the preferred option for sedation of children and adolescents with

cerebral palsy and that the cost of a sedative injection would have minimal impact on the ICER.

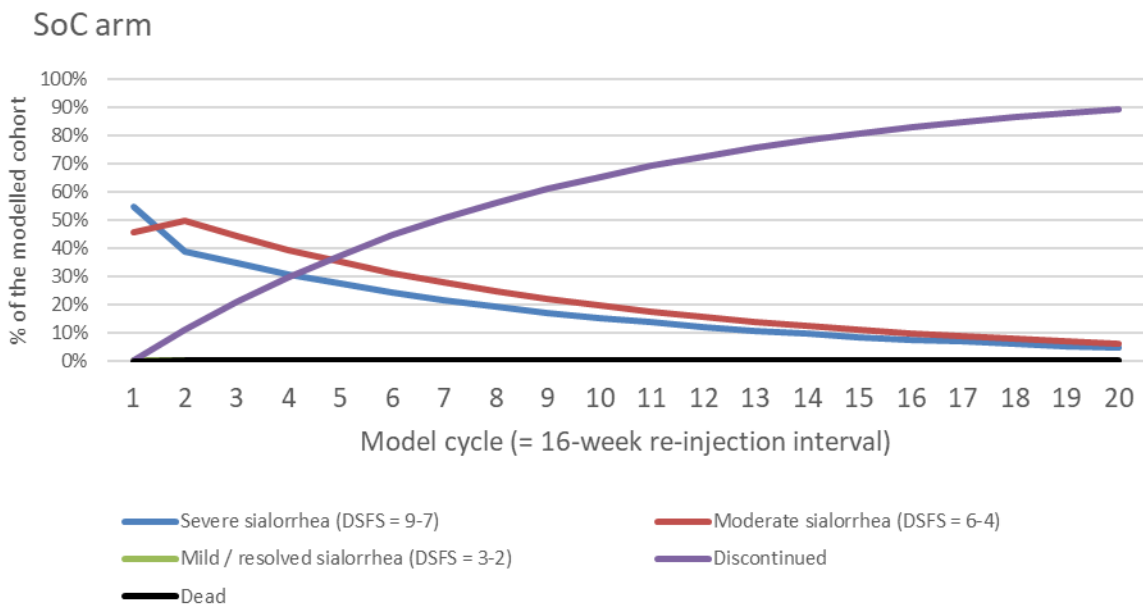
- 6.93 Figure 2 and Figure 4 present the Markov traces of all health states for the incobotulinumtoxinA arm for adults and children and adolescents, respectively. The incobotulinumtoxinA arm was based on trial-based data until 64 weeks (Cycle 1–Cycle 4). Initially, the proportion of patients in the moderate and mild/resolved health states increased as patients moved from severe to moderate, or moderate to mild/resolved. This approach assumed patients continued treatment with improved DSFS score below 6. From 64 weeks (Cycle 4), the model assumed that there were no further transitions between the health states if the patient remained on treatment. A discontinuation rate of 3.09% was applied.
- 6.94 Figure 3 and Figure 5 present the Markov traces of all health states for the SoC arm for adults and children and adolescents. The SoC arm was based on trial-based data up to 16 weeks (Cycle 1). Initially, the proportion of patients in the moderate health state slightly increased and the proportion of patients in the severe health state slightly decreased, the submission claimed that this may reflect the placebo effect. At baseline, there were no patients in the mild health state. From 16 weeks (Cycle 1), the model assumed that there were no further transitions between the health states if the patient remained on treatment. A discontinuation rate of 11.1% was applied. The ESC considered that it is generally not possible to discontinue SoC, particularly as SoC was assumed to consist of non-pharmacological interventions, such as using bibs or other clothing to wipe of saliva and other physical therapy such as posture adjustment, oral motor exercises. In this case, surgery or radiotherapy may be considered as a later line of therapy. However, the cost/effect of later line therapy options were not considered as part of the economic model.

Figure 2: Adults- Markov traces of the incobotulinumtoxinA arm



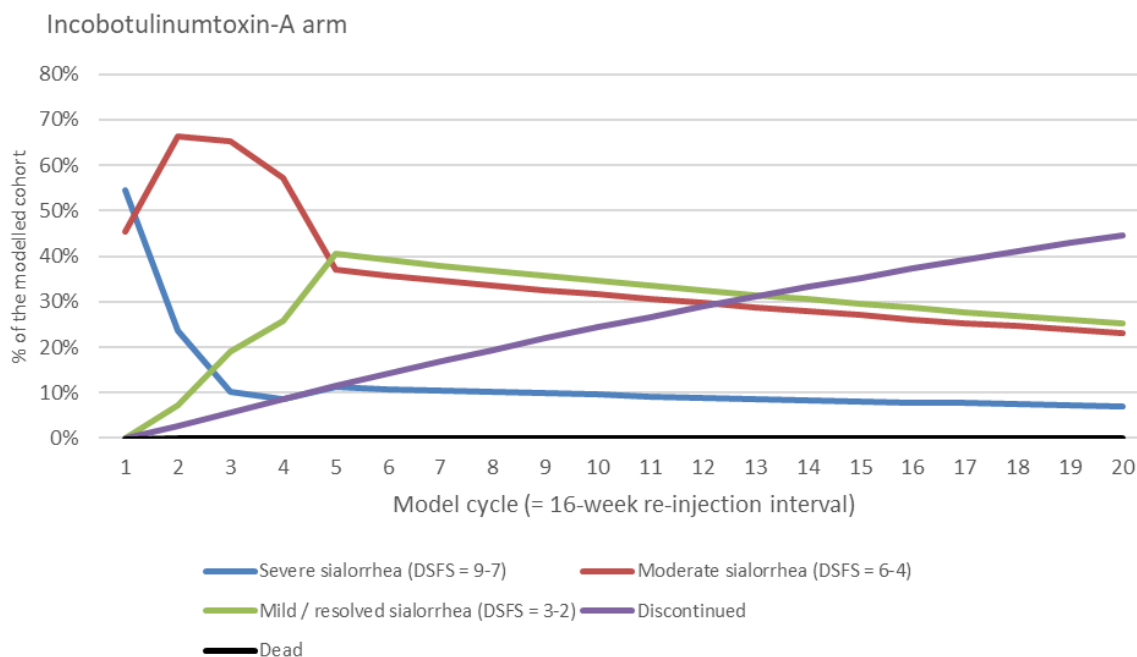
Source: Sheet "Results" of the submitted adult economic model "Xeomin CE analysis SIALORRHEA FINAL 2024 PBAC submission adult population FINAL.xlsx".
 DSFS = Drooling Severity and Frequency Scale.

Figure 3: Adults- Markov traces of the SoC arm



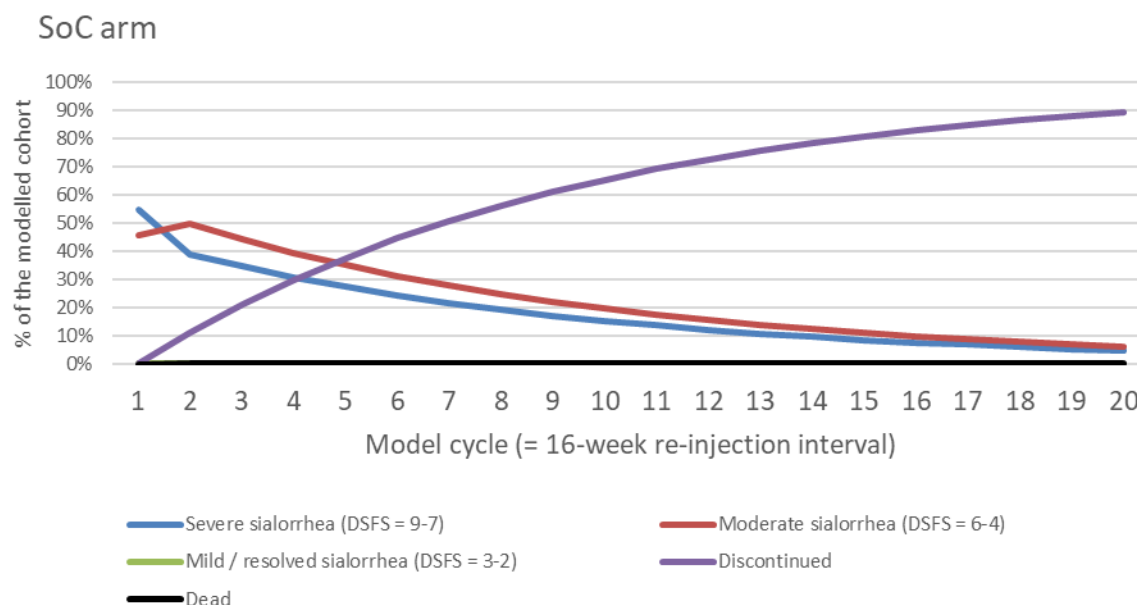
Source: Sheet "Results" of the submitted adult economic model "Xeomin CE analysis SIALORRHEA FINAL 2024 PBAC submission adult population FINAL.xlsx".
 The line indicating for mild/resolved is covered by the line indicating the dead health state.
 DSFS = Drooling Severity and Frequency Scale.

Figure 4: Children and adolescents: Markov traces of the incobotulinumtoxinA arm



Source: Sheet "Results" of the submitted adult economic model "Xeomin CE analysis SIALORRHEA FINAL 2024 PBAC submission paediatric population FINAL.xlsx".
DSFS = Drooling Severity and Frequency Scale.

Figure 5: Children and adolescents: Markov traces of the SoC arm

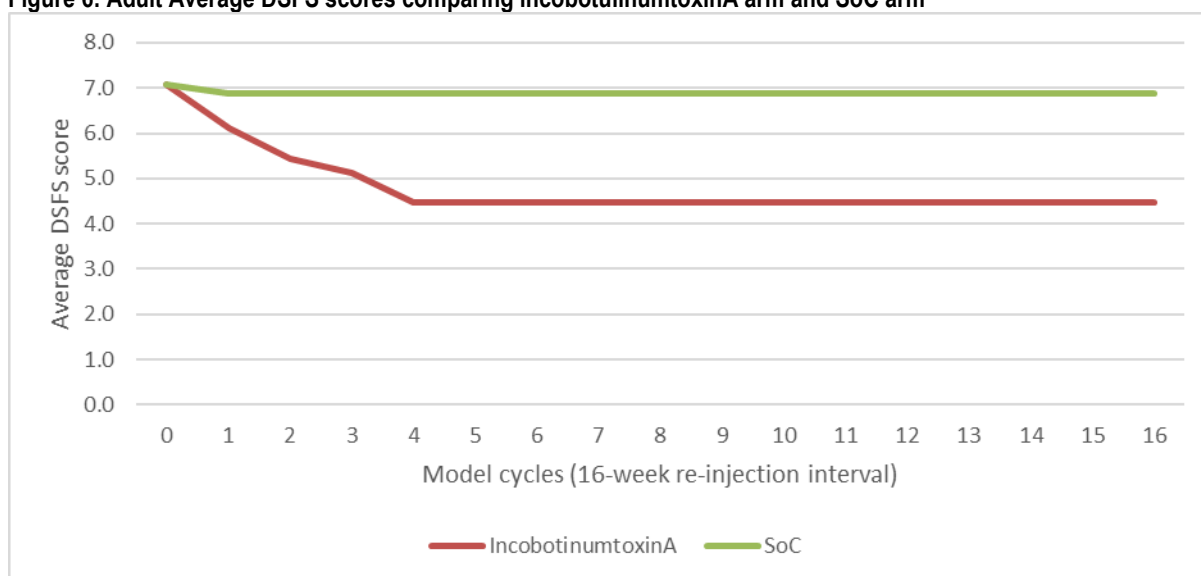


Source: Sheet "Results" of the submitted adult economic model "Xeomin CE analysis SIALORRHEA FINAL 2024 PBAC submission paediatric population FINAL.xlsx".
The line indicating for mild/resolved is covered by the line indicating the dead health state.
DSFS = Drooling Severity and Frequency Scale.

6.95 Figure 6 shows the treatment effect between incobotulinumtoxinA and SoC in the adult model. The average DSFS score reduced from 7.1 in Cycle 1 to 4.5 by Cycle 4 in

the incobotulinumtoxinA arm. This suggested the treatment effect of incobotulinumtoxinA increased over time until Cycle 4 (64 weeks), and then stabilised. The average DSFS score in the SoC arm decreased to 6.9 in Cycle 1. The constant average DSFS scores from Cycle 1 for SoC and Cycle 4 for incobotulinumtoxinA reflects the assumption that patients did not transition between the DSFS severity health states after Cycles 1 and 4 respectively. Consequently, the model assumed that the treatment effect does not wane over time after repeated injections. As discussed previously, this was likely not reasonable (paragraph 6.82).

Figure 6: Adult Average DSFS scores comparing incobotulinumtoxinA arm and SoC arm



Source: Compiled during the evaluation using the mid-point of each severity range and multiplied by the weighed proportion in that severity group, based on the submitted adult economic model "Xeomin CE analysis SIALORRHEA FINAL 2024 PBAC submission adult population FINAL.xlsx".
SoC = Standard of Care.

6.96 Table 13 presents the key drivers of the model.

Table 13: Key drivers of the model

Description	Method/Value	Impact Base case: Adults: \$ ¹ /QALY gained Children and adolescents: \$ ¹ /QALY gained
Time horizon	The time horizon in the model (5 years) was long compared to the duration of follow-up in the SIAXI trial (median 64 weeks).	High. Assuming a time horizon of 16 weeks increased the ICER to \$ ² /QALY gained in the adult model, and \$ ³ /QALY gained in the children and adolescent model.
Treatment waning	The model assumed no further transitions between health states from Cycle 4 as long as the patient remained on treatment. This approach assumed that treatment efficacy did not wane over time after repeated injections.	It was likely not reasonable to assume that treatment effect did not wane due to the lack of data beyond 64 weeks. The economic model was not structured to enable variations to treatment waning.
Utilities	Children and adolescent utility values were assumed to be the same as adult utility values.	High. Applying the lower 95% CI of the utility values increased the ICER to \$ ⁴ /QALY gained in adults and \$ ⁵ /QALY gained in children and adolescents.
Disutilities	No disutilities associated with adverse events were applied in the model (adult and children and adolescents)	Moderate. No disutilities associated with adverse events were applied in the model. However, the impact of adverse events on utilities were captured in the average utility values collected during the trials. Using these values resulted in the ICER increasing to \$ ⁴ /QALY gained in the adult model, and \$ ⁴ in the children and adolescent model.

Source: Table 3.9.2, p104 of the submission.

CI = confidence interval; DSFS = Drooling Severity and Frequency Scale; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life years.

The redacted values correspond to the following ranges:

1 \$25,000 to < \$35,000

2 \$75,000 to < \$95,000

3 \$95,000 to < \$115,000

4 \$35,000 to < \$45,000

5 \$45,000 to < \$55,000

6.97 Table 14 presents the results of the stepped economic evaluation for the adult population and additional stepped analyses conducted during the evaluation. As no mortality gain was modelled, there would be no impact on the life years gained.

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Table 14: Results of the stepped economic evaluation – adult model

Step and component	ICBT-A	Standard of care	Increment
Presented in the submission			
Step 1: 1 year time horizon, all QALYs and costs calculated, discount rate applied.			
Costs	\$	\$385	\$
QALYs	0.78	0.73	0.05
Incremental cost/extra QALY gained			\$ ¹
Step 2: 2-year time horizon, all QALYs and costs calculated, discount rate applied.			
Costs	\$	\$630	\$
QALYs	1.36	1.24	0.11
Incremental cost/extra QALY gained			\$ ²
Step 3: Base case 5-year time horizon, all QALYs and costs calculated, discount rate applied.			
Costs	\$	\$1,285	\$
QALYs	3.02	2.75	0.27
Incremental cost/extra QALY gained (base case)			\$ ³
Conducted during the evaluation			
Step 1a: 16-week time horizon and trial-based utilities by treatment arms, no discount rate applied ^b			
Costs	\$	\$201	\$
QALYs	0.39	0.36	0.03
Incremental cost/extra QALY gained			\$ ¹
Step 2a: 16-week time horizon and trial-based utilities by DSFS severity, no discount rate applied ^c			
Costs	\$	\$201	\$
QALYs	0.38	0.37	0.02
Incremental cost/extra QALY gained			\$ ⁴
Step 3a: 64-week time horizon, costs and trial-based utilities by DSFS severity, no discount rate applied			
Costs	\$	\$473	\$
QALYs	0.99	0.91	0.08
Incremental cost/extra QALY gained			\$ ²
Step 4a: 5-year time horizon, trial-based utilities by DSFS severity, no discount rate applied.			
Costs	\$	\$1,285	\$
QALYs	3.31	3.02	0.29
Incremental cost/extra QALY gained			\$ ³
Step 5a: 5-year time horizon, trial-based utilities by DSFS severity, discount rate applied.			
Costs	\$	\$1,285	\$
QALYs	3.02	2.75	0.27
Incremental cost/extra QALY gained (base case)			\$ ³

Source: Table 3.8.3, p100 of the submission.

a Steps analysis conducted during the evaluation were presented in italics.

b utility values based on trial arms (ignoring DSFS scores): incobotulinumtoxinA arm= 0.63, SoC= 0.59

utility values based DSFS scores both arms are the same, severe (7-9)= 0.55, moderate (4-6)= 0.64; mild/resolved (2-3)= 0.74, baseline=0.59; Cells modified in the adult economic model "Xeomin CE analysis SIALORRHEA FINAL 2024 PBAC submission adult population FINAL.xlsx", to estimate the step analyses: sheet: "Xeomin+SoC Markov'BY74, BP 74, CM74, "SoC Markov'BY74, BP 74, CM74. DSFS = Drooling Severity and Frequency Scale; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life years; SoC= Standard of Care; ICBT-A = IncobotulinumtoxinA

The redacted values correspond to the following ranges:

1 \$45,000 to < \$55,000

2 \$35,000 to < \$45,000

3 \$25,000 to < \$35,000

4 \$75,000 to < \$95,000

6.98 The estimated ICER in the base case was \$25,000 to < \$35,000 per QALY gained for the adult population. The step that had the greatest impact on the result was increasing the time horizon from 16-weeks to 64-weeks (Step 2a to 3a).

6.99 The results for the adult population should be considered with caution because:

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- The time horizon in the model (5 years) was long compared to the duration of follow-up in the SIAXI trial (median 64 weeks). The model also assumed that treatment efficacy did not wane with prolonged treatment. It was likely unreasonable to assume that treatment effect did not wane over time after repeated injections, particularly given the lack of data beyond 64 weeks.
- The use of the DSFS to determine transition probabilities has several issues including that it lacks psychometric and statistical/clinical validation, is rarely used in clinical practice and does not capture the impact of drooling on daily activities, quality of life or emotional distress (see paragraph 3.8).
- No disutilities associated with adverse events were applied in the model.

6.100 Table 15 presents the results of the stepped economic evaluation for the children and adolescent population and additional stepped analyses conducted during the evaluation. As no mortality gain was modelled, there would be no impact on life years gained.

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Table 15: Results of the stepped economic evaluation - children and adolescents

Step and component	ICBT-A	SoC	Increment
Presented in the submission			
Step 1: 1 year time horizon, all QALYs and costs calculated, discount rate applied.			
Costs	\$	\$387	\$
QALYs	0.78	0.73	0.05
Incremental cost/extra QALY gained			\$ ¹
Step 2: 2-year time horizon, all QALYs and costs calculated, discount rate applied.			
Costs	\$	\$636	\$
LYG	1.36	1.26	0.11
Incremental cost/extra QALY gained			\$ ²
Step 3: Base case 5-year time horizon, all QALYs and costs calculated, discount rate applied.			
Costs	\$	\$1,317	\$
QALYs	3.08	2.82	0.25
Incremental cost/extra QALY gained (base case)			\$ ²
Conducted during the evaluation			
Step 1a: 16-week time horizon and trial-based utilities by treatment arms, no discount rate applied^b			
Costs	\$	\$201	\$
QALYs	0.39	0.37	0.02
Incremental cost/extra QALY gained			\$ ¹
Step 2a: 16-week time horizon and trial-based utilities by DSFS severity, no discount rate applied^c			
Costs	\$	\$201	\$
QALYs	0.38	0.37	0.02
Incremental cost/extra QALY gained			\$ ³
Step 3a: 64-week time horizon and trial-based utilities by DSFS severity, no discount rate applied			
Costs	\$	\$476	\$
QALYs	0.99	0.92	0.07
Incremental cost/extra QALY gained			\$ ⁴
Step 4a: 5-year time horizon, trial-based utilities by DSFS severity, no discount rate applied.			
Costs	\$	\$1,438	\$
QALYs	3.38	3.10	0.28
Incremental cost/extra QALY gained			\$ ⁵
Step 5a: 5-year time horizon, trial-based utilities by DSFS severity, discount rate applied.			
Costs	\$	\$1,317	\$
QALYs	3.08	2.82	0.25
Incremental cost/extra QALY gained (base case)			\$ ²

Source: Table 3.8.2, p100 of the submission.

a Steps analysis conducted during the evaluation were presented in italics.

b utility values based on trial arms (ignoring DSFS scores): incobotulinumtoxinA arm= 0.63, SoC= 0.59

c: utility values based DSFS scores both arms are the same, severe (7-9) =0.55, moderate (4-6)= 0.64; mild/resolved (2-3)= 0.74, baseline=0.59; Cells modified in the adult economic model "Xeomin CE analysis SIALORRHEA FINAL 2024 PBAC submission adult population FINAL.xlsx", to estimate the step analyses: sheet: "Xeomin+SoC Markov'BY74, BP 74, CM74, "SoC Markov'BY74, BP 74, CM74. DSFS = Drooling Severity and Frequency Scale; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life years; SoC= Standard of Care; ICBT-A = IncobotulinumtoxinA

The redacted values correspond to the following ranges:

1 \$55,000 to < \$75,000

2 \$35,000 to < \$45,000

3 \$95,000 to < \$115,000

4 \$45,000 to < \$55,000

5 \$25,000 to < \$35,000

6.101 The estimated ICER in the base case was \$45,000 to < \$55,000 per QALY gained for the children and adolescent population. The step that had the greatest impact on the result was increasing the time horizon from 16-weeks to 64-weeks (Step 2a to 3a).

- 6.102 The results for the children and adolescent population should be considered with caution because, in addition to the issues identified for the adult population model:
- The use of adult data to estimate transition probabilities and utilities increased uncertainty in the results, especially given the different patient populations.
- 6.103 Table 16 summarises the key sensitivity analyses presented in the submission and additional sensitivity analyses conducted during the evaluation.

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Table 16: Key sensitivity analyses for adult and children and adolescent models

Analyses	Incremental cost	Incremental QALY	ICER
Adults			
Base case	\$	0.27	\$ ¹
Discount rate (base case 5% costs and outcomes)			
• 0% costs and outcomes	\$	0.29	\$ ¹
• 3.5% costs and outcomes	\$	0.27	\$ ¹
Time horizon (base case 5 years)			
• 16 weeks	\$	0.02	\$ ²
• 1 year	\$	0.07	\$ ³
• 64 weeks	\$	0.05	\$ ⁴
• 2 years	\$	0.11	\$ ⁴
• 10 years	\$	0.40	\$ ⁵
Response based stopping rule ^b from 1 cycle	\$	0.24	\$ ¹
Response based stopping rule ^b from 2 cycles	\$	0.25	\$ ¹
Average trial-based utilities per treatment arm ^a	\$	0.21	\$ ⁴
Utilities Lower 95% CI ^d	\$	0.18	\$ ⁴
No treatment discontinuation in SoC arm (base case = 11.0%)	\$	0.24	\$ ¹
Multivariate analyses			
16-week time horizon, trial-based utilities by treatment arms (ignoring DSFS severity score) ^a	\$	0.03	\$ ³
64-week time horizon, trial-based utilities by treatment arms (ignoring DSFS severity score) ^a	\$	0.07	\$ ⁴
Children and adolescents			
Base case	\$	0.25	\$ ⁴
Discount rate (base case 5% costs and outcomes)			
• 0% costs and outcomes	\$	0.2796	\$ ¹
• 3.5% costs and outcomes	\$	0.2608	\$ ⁴
Time horizon (base case 5 years)			
• 16 weeks	\$	0.02	\$ ⁵
• 1 year	\$	0.05	\$ ⁶
• 64 weeks	\$	0.07	\$ ³
• 2 years	\$	0.11	\$ ⁴
• 10 years	\$	0.39	\$ ¹
Response based stopping rule ^b from 1 cycle	\$	0.24	\$ ⁴
Response based stopping rule ^b from 2 cycles	\$	0.25	\$ ⁴
Utilities derived estimates via regression model ^e	\$	0.40	\$ ⁷
Average trial-based utilities per treatment arm ^a	\$	0.21	\$ ⁴
Utilities Lower 95% CI ^d	\$	0.17	\$ ³
No treatment discontinuation in SoC arm	\$	0.23	\$ ⁴
Including anaesthesia costs for children and adolescents ^c	\$	0.25	\$ ⁴
Multivariate analyses			
16-week time horizon, trial-based utilities by treatment arms (ignoring DSFS severity score) ^a	\$	0.02	\$ ⁶
64-week time horizon, trial-based utilities by treatment arms (ignoring DSFS severity score) ^a	\$	0.05	\$ ⁶

Source: Table 3.9.2, p104 of the submission. Sensitivity analyses conducted during the evaluation are presented in italics.

CI = confidence interval; DSFS = Drooling Severity and Frequency Scale; ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life years; SoC = Standard of Care.

a Average utility value was 0.63 in the incobotulinumtoxinA arm and 0.59 in the SoC arm.

b Response based stopping rule whereby only patients satisfactorily responding to the treatment are eligible for ongoing subsidisation

c Total anaesthesia costs: \$162.50, including anaesthesia brief consultation: MBS 17610= \$49.75; anaesthesia fees: 1:01 HOURS to 1:15 HOURS, MBS 23055=\$112.75

d Utility values based DSFS scores both arms are the same, severe (7-9) = 0.55, moderate (4-6) = 0.64; mild/resolved (2-3) = 0.74, baseline

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= 0.59; Utilities lower 95% CI: severe (7-9) = 0.50, moderate (4-6) = 0.61; mild/resolved (2-3) = 0.63, baseline = 0.55

The redacted values correspond to the following ranges:

- 1 \$25,000 to < \$35,000
- 2 \$75,000 to < \$95,000
- 3 \$45,000 to < \$55,000
- 4 \$35,000 to < \$45,000
- 5 \$95,000 to < \$115,000
- 6 \$55,000 to < \$75,000
- 7 \$15,000 to < \$25,000

6.104 The model was most sensitive to the time horizon and applying average utilities to each treatment arm (rather than estimating utilities by DSFS severity score).

IncobotulinumtoxinA cost/patient/year

Table 17: Drug cost per patient for IncobotulinumtoxinA

	ICBT-A						
	Adults			Children and adolescents			
	Trial dose and duration	Model	Financial estimates	Trial dose and duration		Model	Financial estimates
6-17 years				2-5 years			
Dose	100U	100U	100U	100U	100U	100U	100U
Mean duration ^a	16.13 weeks	101 weeks (6.3 cycles)	121 weeks (7.5 cycles)	Median: 16.1 weeks	Median: 16.7 weeks	104 weeks (6.5 cycles)	121 weeks (7.5 cycles)
Scripts/year	N/A	3.3 ^b	3	N/A	N/A	3.3 ^b	3
Cost/patient/ trial-based period (16 weeks)	\$379.17	\$379.17	\$379.17	\$379.17	\$379.17	\$379.17	\$379.17
Total cost/ patient/year	N/A	\$1,011.11 ^c	\$1,137.51 ^d	N/A	N/A	\$1,034.23 ^c	\$1,137.51 ^d

Source: Compiled during the evaluation based on Table 1.4.1, p23 of the submission; pp181-182 of the SIAXI trial CSR; p129 of the SIPEXI trial CSR; sheet 'Xeomin+SoC Markov' of the adult and paediatric economic models; sheets '2a. Patients – incident', '2b. Patients – prevalent', and '3a. Scripts – proposed' of the financial estimates. Italicised text calculated during the evaluation using the economic model and financial estimates spreadsheets.

100U = 100 units.

^a Mean cycle length was not presented for the SIPEXI trial. Modelled duration (including discontinuations) was the average proportion of patients on treatment (column U, sheet 'Xeomin+SoC Markov') in each cycle to time horizon (4.92 years). Financial estimates duration (excluding discontinuations) was the weighted average of patients commencing in Years 1-6 receiving 6 to one years' treatment.

^b Economic model was based on 16-week cycles. Cycles per year = 365.25/7/16

^c Sum of modelled medicine costs (column BL, sheet 'Xeomin+SoC Markov') to time horizon (4.92 years)/4.92

^d The financial estimates assumed no discontinuation. Total cost/patient/year = 3 * \$379.17

ICBT-A = IncobotulinumtoxinA

6.105 At the proposed DPMQ of \$379.17, the total cost of incobotulinumtoxinA 100U per course (16 weeks) was \$379.17. SoC did not incur any drugs cost during the trial period, the economic model, or financial estimates.

6.106 The financial estimates did not consider discontinuations. The financial estimates therefore implicitly assumed that patients commencing treatment in Year 1 received 6 years of treatment over 6 years, patients commencing treatment in Year 2 received 5 years of treatment, and so on. The mean duration of treatment in the financial estimates was therefore longer the mean duration of treatment estimated in the economic models.

6.107 The estimated total cost of incobotulinumtoxinA 100U per patient per year was \$1,011.11 in the economic model for adults and \$1,034.23 in the economic model for

children and adolescents. This was lower than the estimated total cost in the financial estimates for adults and children and adolescents (\$1,137.51).

6.108 Dosage in children and adolescents ranged from 20U (body weight: ≥ 12 and < 15 kgs) to 75U (≥ 30 kgs). There was potential wastage as each vial contained 100U, with the remaining units being discarded. The submission accounted for wastage in the economic model.

Estimated PBS usage & financial implications

6.109 This submission was considered by DUSC.

6.110 The submission used an epidemiological approach to estimate the financial impact of the proposed medicine.

6.111 The financial and the economic models applied MBS costs associated with the administration of incobotulinumtoxinA to adults, children and adolescents. The MBS item nominated in the submission (MBS item 18374 for the treatment of bilateral blepharospasm) was unlikely to capture the complexities and associated costs of treating this cohort of patients. Additionally, the MBS costs of adult patients would potentially be different to those for children and adolescents as the economic model did not include anaesthetic fees, which could be complex to estimate given that there are inpatient and outpatient benefits to anaesthetic benefits and potential costs to the health care system from day admissions. Some children, adolescents, and patients with Parkinson’s disease and traumatic brain injury may also need sedation, which is associated with a cost to the healthcare system.

6.112 Table 18 presents the key inputs relied on in the financial estimates.

Table 18: Key inputs for financial estimates

Parameter	Value	Source	Comment
Prevalence and incidence of Parkinson’s disease, atypical Parkinson’s, TBI, and stroke in adults, and cerebral palsy, TBI and developmental disorder in children and adolescents	Various	Various published sources	-
Percentage of adults with the specified neurological conditions presenting with chronic sialorrhea	16%	Survey from clinicians	This was uncertain. The DUSC noted that this parameter varied by condition and commented that it was unclear why the submission applied one overall figure to all neurological conditions. The DUSC considered the lower value for Parkinson’s disease may be more reasonable given this condition represents the largest population affected by chronic sialorrhea (70.7% in the SIAXI trial). The DUSC noted that the financial estimates were sensitive to this parameter.

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Parameter	Value	Source	Comment
Percentage of children and adolescents with the specified neurological conditions presenting with chronic sialorrhea	11.0%	Survey from clinicians	The DUSC considered this parameter was uncertain and was likely underestimated. A systematic review stated that 11% to 50% of children with cerebral palsy may experience chronic sialorrhea (Dias et al. 2016). Thus, the submission may have underestimated the number of eligible patients. A sensitivity analysis assuming 50% of children and adolescents with cerebral palsy experience chronic sialorrhea was conducted during the evaluation.
Percentage of adult stroke patients and TBI patients in both adult and children and adolescents	12%	Gozalez-Fernandez et al. 2013	The submission assumed that 12% of stroke and TBI patients would experience chronic sialorrhea, but also applied an additional 16% based on a clinician survey to reflect the adult population who would experience chronic sialorrhea. Consequently, the submission double-counted the proportion of patients experiencing chronic sialorrhea, and thus underestimated the number of eligible patients for 3 disease conditions: adults with stroke, adults with TBI, and children and adolescents with TBI. This calculation has been revised throughout the evaluation.
Uptake rate	Ranged between 0.5% - 10% from Yr1 to Yr6.	Overseas market	The source was reasonable; however, the DUSC considered that treatment uptake may be higher as Australian specialists are already familiar with incobotulinumtoxinA and are using it off-label.
Duration of treatment	121 weeks (7.5 cycles)	Calculated during the evaluation	The financial estimates did not consider discontinuations. The financial estimates therefore implicitly assumed that patients commencing treatment in Year 1 received 6 years of treatment, patients commencing treatment in Year 2 received 5 years of treatment, and so on. The mean duration of treatment in the financial estimates was therefore longer than the mean duration of treatment estimated in the economic models. The DUSC noted the uncertainty regarding treatment duration given the adverse events of dry mouth and dysphagia associated with treatment.

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Parameter	Value	Source	Comment
Costs			
IncobotulinumtoxinA	\$379.17	Proposed DPMQ	-
Consultation fee, injection fee, ultrasound fee	\$87.30	MBS item 116, 18374 and 55848	MBS costs associated with the administration of incobotulinumtoxinA to adults, children and adolescents. The MBS item nominated in the submission (MBS item 18374 for the treatment of bilateral blepharospasm) was unlikely to capture the complexities and associated costs of treating this cohort of patients. Anaesthesia costs were not included for children and adolescents which did not align with the SIPEXI trial, in which general anaesthesia was offered to all children. The DUSC considered that some children, adolescents, and patients with Parkinson's disease and traumatic brain injury may need sedation, which is associated with a cost to the healthcare system. The DUSC also noted that additional costs such as staff, medication and monitoring were not accounted for in the financial estimates.
Proportion of adults requiring ultrasound	55%	SIAXI trial	This was consistent with the SIAXI trial population.
Proportion of children and adolescents requiring ultrasound	100%	SIPEXI trial	This was consistent with the TGA product information.
Patient co-payment	PBS: \$7.73 RPBS: \$4.45	Calculated based on all PBS item codes to estimate the proportion of PBS services vs RPBS services	This was not appropriate. The submission should have used the incobotulinumtoxinA listed PBS items for cervical dystonia (10994P), blepharospasm (11005F) and spasticity (12087E) of the upper limb to estimate the proportion of PBS services vs RPBS services. Based on this method: PBS: \$19.56 RPBS: \$7.50
PBS/RPBS Split	PBS: 96.97% RPBS: 3.03%	Calculated based on all PBS item codes to estimate the proportion of PBS services vs RPBS services	This was not appropriate. The submission should have used the incobotulinumtoxinA listed PBS items for cervical dystonia (10994P), blepharospasm (11005F) and spasticity (12087E) of the upper limb to estimate the proportion of PBS services vs RPBS services. Based on this method: PBS: 98.19% RPBS: 1.81%

Source: Table 4.2.6, p113, Table 4.2.3, p111, and Table 4.3.5, p112 of the submission.

DPMQ= Dispensed Price for Maximum Quantity; MBS = Medicare Benefits Schedule; PBS= Pharmaceutical Benefits Scheme; PI= Product information; RPBS= Repatriation Pharmaceutical Benefits Scheme; TBI = Traumatic Brain Injury.

6.113 The submission estimated the number of adults and children and adolescents with 7 neurological diseases using prevalence and incidence rates. The conditions by population were:

- Parkinson's disease – adults,

- Atypical Parkinson's disease – adults,
- Traumatic Brain Injury (TBI) – adults,
- Stroke – adults,
- Cerebral palsy – children and adolescents,
- Traumatic Brain Injury (TBI) – children and adolescents,
- Developmental disorder – children and adolescents.

6.114 These 7 neurological diseases were based on the SIAXI and SIPEXI trial populations. However, the submission requested that the PBAC consider PBS listing incobotulinumtoxinA for a broader population (see paragraph 3.13). The DUSC considered that it was unclear why the submission requested that PBAC consider extending the restriction to include other health conditions, such as adults with cerebral palsy and motor neuron disease, given the lack of clinical data presented in the submission for these conditions. The pre-PBAC response stated that a broad PBS listing would align with the TGA indication and aligns with current clinical practice. The Response noted that input from expert clinicians indicated that adults with cerebral palsy and patients with motor neurone disease in particular would greatly benefit from treatment with incobotulinumtoxinA. The Response also noted that the safety and efficacy of incobotulinumtoxinA is well established in children/adolescents with cerebral palsy in the SIPEXI trial, and it is reasonable to assume they would continue to receive benefit in adulthood.

6.115 The net cost to the PBS/RPBS and the healthcare budget are described in Table 19

6.116 There was a calculation error in the number of scripts as the submission included both PBS and RPBS scripts when estimating scripts for PBS. The calculation of the PBS script volumes and total volumes were incorrect for both the adult and children and adolescent populations (sheet 3a. Scripts proposed, cell F50 to K50 and F51 to K51, F73 to K73). In addition, the submission assumed that 12% of stroke and TBI patients would experience chronic sialorrhea, but also applied an additional 16% based on a clinician survey to reflect the adult population who would experience chronic sialorrhea. Consequently, the submission double-counted the proportion of patients experiencing chronic sialorrhea, and thus underestimated the number of eligible patients for 3 disease conditions: adults with stroke, adults with TBI, and children and adolescents with TBI. After removing double counting, the total incobotulinumtoxinA prescriptions was estimated in the evaluation to be 500 to < 5,000 in Year 1 and increased to 40,000 to < 50,000 in Year 6, a total of 100,000 to < 200,000 prescriptions over 6 years.

Table 19: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Revised estimated extent of use ^a						
Estimated extent of use						
Number of patients treated	¹	¹	¹	²	³	³
Number of scripts dispensed	¹	²	³	⁴	⁵	⁵
Estimated financial implications of incobotulinumtoxinA						
Cost to PBS/RPBS less copayments	\$ ⁶	\$ ⁶	\$ ⁶	\$ ⁶	\$ ⁷	\$ ⁷
Net financial implications						
Net cost to PBS/RPBS (\$)	\$ ⁶	\$ ⁶	\$ ⁶	\$ ⁶	\$ ⁷	\$ ⁷
Net cost to MBS	\$ ⁶	\$ ⁶	\$ ⁶	\$ ⁶	\$ ⁶	\$ ⁶
Net cost to Australian Government	\$ ⁶	\$ ⁶	\$ ⁶	\$ ⁷	\$ ⁸	\$ ⁸

Source: sheet "3a. Scripts – proposed" – financial workbook; Table 4.3.7, p119 of the submission; Table 4.5.1, p120 of the submission; Table 4.6.1, p120 of the submission. MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

^a Revised estimates based on Xeomin_Sialorrhoea_UCM-Release-3-Workbook-v1081.xlsx(sheet 3a. Scripts proposed, cell F50 to K50 and F51 to K51, F73 to K73). And removed double counting for stroke patients in adults and TBI patients in both adults and children and adolescents.

The redacted values correspond to the following ranges

1 500 to < 5,000

2 5,000 to < 10,000

3 10,000 to < 20,000

4 20,000 to < 30,000

5 40,000 to < 50,000

6 \$0 to < \$10 million

7 \$10 million to < \$20 million

8 \$20 million to < \$30 million

6.117 Dosage in children and adolescents ranged from 20U (body weight: ≥12 and <15 kgs) to 75U (≥30 kgs). There was potential wastage as each vial contained 100U, with the remaining units being discarded. The submission included the wastage when estimating the total cost to the PBS/RPBS.

6.118 The estimated net cost of listing incobotulinumtoxinA to the PBS/RPBS was estimated to be \$40 million to < \$50 million over 6 years.

6.119 The total net cost to the Australian Government was estimated to be \$0 to < \$10 million in Year 1, increase to \$20 million to < \$30 million in Year 6, and total \$70 million to < \$80 million over the first 6 years of listing.

6.120 The evaluation considered that the expected uptake rate was uncertain and may be underestimated. The PSCR argued that the slower uptake in the initial years of listing was based on evidence in overseas markets where awareness of the indication and treatment was found to be low upon listing and only grew once doctors received additional training and the treatment became more available across the market. The PSCR stated that the same issues with training and awareness were likely and therefore, a slower uptake once listed would be expected. The PSCR also noted that the PBS listing of incobotulinumtoxinA for chronic sialorrhoea would not increase the total number of approved injectors in Australia. With the addition of a new indication, injectors would be required to treat additional patients, likely slowing down all

botulinum toxin treatments. The DUSC noted treatment uptake of botulinum toxin had been lower than projected in other indications. However, the DUSC considered the treatment uptake rate of incobotulinumtoxinA for chronic sialorrhea could be greater than estimated by the submission as clinicians would not require training as they would be familiar with its use off-label, particularly for patients in palliative care.

- 6.121 The pre-PBAC Response maintained that uptake is expected to be lower in the initial years of listing and would likely grow as specialists become more familiar with the treatment. The Response stated that of the clinicians expected to treat patients with incobotulinumtoxinA, only neurologists and rehabilitation specialists were currently familiar with administering botulinum toxin items. The Response stated that geriatricians, paediatricians, ENT surgeons and plastic surgeons are expected to require additional training as they are not frequent users of botulinum toxin. However, the Response stated it would accept a higher uptake rate to mitigate any remaining uncertainty related to the projected eligible population. The Response stated that when adopting a 20% increase to the base case uptake rates resulted in the net cost to the PBS/RPBS increasing from \$40 million to < \$50 million to \$50 million to < \$60 million over the first six years of listing.
- 6.122 Overall, the DUSC considers the estimates presented in the submission to be underestimated.
- 6.123 The DUSC noted that the financial estimates were sensitive to the uptake rate. The total net cost to the PBS/RPBS increased from \$40 million to < \$50 million to \$50 million to < \$60 million over the 6 years, when applying a 20% increase to the base case uptake rate, or decreased to \$30 million to < \$40 million over the 6 years, when applying a 20% decrease to the base case uptake rate. The total net cost to the PBS/RPBS increased from \$40 million to < \$50 million to \$50 million to < \$60 million over the 6 years with a constant uptake rate of 5%. The total net cost to the PBS/RPBS increased from \$40 million to < \$50 million to \$100 million to < \$200 million over the 6 years with a constant uptake rate of 10%.
- 6.124 The DUSC considered additional sensitivity analyses (Table 20). The DUSC noted that if the proportion of adults presenting with chronic sialorrhea was increased from 16% to 30%, this increased the total net cost to the PBS/RPBS to \$50 million to < \$60 million over the first 6 years of listing.

Table 20: Estimated implications for the net cost to the PBS/RPBS

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Base case	\$ ¹	\$ ¹	\$ ¹	\$ ¹	\$ ¹	\$ ¹
Base case (revised calculation)	\$ ¹	\$ ¹	\$ ¹	\$ ¹	\$ ²	\$ ²
Uptake rate – Upper (increased by 20%)	\$ ¹	\$ ¹	\$ ¹	\$ ²	\$ ²	\$ ²
Uptake rate - Lower (decreased by 20%)	\$ ¹	\$ ¹	\$ ¹	\$ ¹	\$ ²	\$ ²
Including adult cerebral palsy patients	\$ ¹	\$ ¹	\$ ¹	\$ ¹	\$ ²	\$ ²
50% of children and adolescents cerebral palsy patients experiencing chronic sialorrhea	\$ ¹	\$ ¹	\$ ¹	\$ ¹	\$ ²	\$ ²
Uptake rate: constant 5% increase	\$ ¹	\$ ¹	\$ ¹	\$ ¹	\$ ¹	\$ ¹
Uptake rate: constant 10% increase	\$ ³	\$ ³	\$ ³	\$ ³	\$ ³	\$ ³
PBS vs RPBS: 98.19% vs 1.81%	\$ ¹	\$ ¹	\$ ¹	\$ ²	\$ ⁴	\$ ⁴
30% of adults with the specified neurological conditions presenting with chronic sialorrhea	\$ ¹	\$ ¹	\$ ¹	\$ ²	\$ ²	\$ ²

Source: Table 4.6.2 of the commentary on the submission.

Revised estimates shown in italics based on Xeomin_Sialorrhea_UCM-Release-3-Workbook-v1081.xlsx(sheet 3a. Scripts proposed, cell F50 to K50 and F51 to K51, F73 to K73). And removed double counting for stroke patients in adults and TBI patients in both adults and children and adolescents.

PBS= Pharmaceutical Benefits Scheme; RPBS= Repatriation Pharmaceutical Benefits

The redacted values correspond to the following ranges

1 \$0 to < \$10 million

2 \$10 million to < \$20 million

3 \$30 million to < \$40 million

4 \$20 million to < \$30 million

Quality Use of Medicines

6.125 The submission stated that the quality use of incobotulinumtoxinA was promoted through:

- Organising and conducting regular workshops with experienced injectors.
- Promoting the use of guidance injection techniques using ultrasound and loan portable ultrasound devices for physicians to familiarise themselves with the technique.
- Provision of the www.saliva.com website, providing information and resources for the treatment of sialorrhea using incobotulinumtoxinA.

6.126 The submission provided limited information regarding the quality use of medicines. The information provided via the website www.saliva.com should indicate that this is information provided by the sponsor and should not be a general information website that consumers could mistake for independent information.

6.127 The DUSC considered that although clinicians would be familiar with botulinum toxin, a recent study demonstrated inaccuracy in blindly administering botulinum toxin to

the salivary glands, particularly the submandibular glands, as such further education on ultrasound-guided injections may be needed for some administering clinicians.¹⁸

- 6.128 The DUSC noted the safety concerns relating to the use of incobotulinumtoxinA for chronic sialorrhea were atrophy of the salivary gland and impaired dental health due to dry mouth. The DUSC stated that dry mouth could lead to complications, including gingivitis, dysphagia and dental caries. The DUSC noted the TGA risk management plan identified atrophy of salivary glands as an important potential risk and recommended the inclusion of incobotulinumtoxinA in the Black Triangle Scheme (TGA AusPAR incobotulinumtoxinA). The ACM also supported including information on dental health within the PI and CMI (TGA AusPAR incobotulinumtoxinA).

For more detail on PBAC's view, see Section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC deferred making a recommendation for the listing of incobotulinumtoxinA for the treatment of chronic sialorrhea due to neurological disorders. While the PBAC was of a mind to recommend incobotulinumtoxinA, the PBAC noted that an MSAC application for the administration of incobotulinumtoxinA for chronic sialorrhea was also required to ensure there would be access to the required MBS items. The PBAC considered that the evidence presented demonstrated an improvement in both the severity and frequency of sialorrhea compared with placebo. However, due to short trial durations and the lack established MCIDs, the magnitude of this benefit was uncertain. The PBAC considered incobotulinumtoxinA was not cost-effective at the price proposed in the submission given optimistic assumptions included in the economic model. The PBAC advised that a price reduction would be required for incobotulinumtoxinA to be considered cost-effective. The PBAC considered that, on balance, the utilisation estimates provided in the submission were reasonable.
- 7.2 The PBAC noted the input from health care professionals and Motor Neurone Disease (MND) Australia highlighting the clinical need for effective PBS-listed options for this population, noting that anticholinergics are associated with significant side effects and botulinum toxin injections are high cost. The PBAC noted the consumer comments emphasising that sialorrhea is a life-altering condition and the important clinical and quality of life benefits that were associated with reduced salivary production in this patient population. The PBAC also noted the input describing the adverse effects associated with incobotulinumtoxinA, including dry mouth and dysphagia, and considered these to be manageable. The comments emphasised, however, the importance that the dosage and administration be conducted by experienced practitioners. The PBAC noted comments stating that the cost of incobotulinumtoxinA remained a financial burden to patients and that a PBS listing would ensure equity of

¹⁸ Marks IH, Ridgley Vaidya J, Israel O, Nixon P, Sharma R. Does injection of botulinum toxin to salivary glands require ultrasound guidance?. *Int J Pediatr Otorhinolaryngol*. Published online September 17, 2024. doi:10.1016/j.ijporl.2024.112114

access.

- 7.3 The PBAC considered there remained a moderate clinical need for additional treatment options for patients with chronic sialorrhea due to neurological disorders.
- 7.4 With regards to the requested listing and restriction, the PBAC advised that it was appropriate for:
- The inclusion of a criterion requiring an improvement of at least one point in the Thomas-Stonell and Greenberg Drooling Severity and Frequency Scale (DSFS) score to continue treatment. The PBAC considered that changes made by the Secretariat with regards to treatment continuation and administrative advice were appropriate.
 - Paediatric patients who initiate treatment for cerebral palsy or developmental disorders to be eligible for continued treatment as an adult. Hence the age criterion, in the paediatric restriction, would change to: 'Patient must be aged from 2 to 17 years inclusive at treatment initiation with this drug'.
 - The removal of the proposed treatment criterion for children and adolescents requiring treatment to be guided by ultrasound as administration of incobotulinumtoxinA is outlined in the TGA production information (PI) and clinical guidelines.
- 7.5 The PBAC also noted that the submission suggested that it may be reasonable to extend the PBS listing criteria to include patients with other neurological conditions known to cause chronic sialorrhea. However, the PBAC advised that the proposed extension to the PBS listing was not appropriate due to the lack of clinical trial evidence.
- 7.6 The PBAC noted that the nominated comparator, standard medical management (standard of care [SoC]), did not align with the proposed treatment algorithm which proposed that incobotulinumtoxinA would replace botulinum toxin type A injections (third-line setting). The PBAC also noted that several anticholinergics have unrestricted PBS listings and are commonly used in clinical practice. However, the PBAC accepted the nominated comparator as reasonable in view of the fact that botulinum toxin type A injections and anticholinergic medications are not currently TGA-approved, or PBS listed, for this indication and their cost-effectiveness has not been previously assessed.
- 7.7 The PBAC noted that the submission was based on 2 head-to-head randomised controlled trials comparing incobotulinumtoxinA to placebo: the SIAXI trial (N=184 adults) and the SIPEXI trial (N=256 children and adolescents). The PBAC noted that the main phase of the trials was 16 weeks, which was not adequate to capture long-term outcomes and adverse events. While acknowledging this limitation, the PBAC considered that the trials adequately demonstrated that incobotulinumtoxinA 100U improved unstimulated Salivary Flow Rate (uSFR) and Global Impression of Change Scale (GICS) compared to placebo from baseline to Week 4. The PBAC also noted that

the mean differences for both outcomes from baseline to Week 4 in both trials were statistically significant. However, the PBAC considered that the clinical significance of the observed benefit was uncertain due to the lack of established or validated minimal clinically important differences (MCIDs) for the outcomes measured in both trials. The PBAC considered that the MCIDs proposed by the submission (uSFR = 0.05 g/min, GICS score = 1.0 point) were uncertain due to a number of limitations, as discussed in paragraphs 6.18 to 6.21, and 6.27. Overall, the PBAC considered the clinical evidence supported the claim of superior comparative effectiveness of incobotulinumtoxinA over placebo; however, due to short trial durations and the lack established MCIDs, the magnitude of this benefit was uncertain.

- 7.8 The PBAC noted that the frequency of treatment-emergent adverse events (TEAEs) (45.9% with incobotulinumtoxinA 100U versus 41.7% with placebo) and treatment-related TEAEs (8.1% with incobotulinumtoxinA 100U versus 8.3% with placebo) was similar between the treatment arms in the main phase of the SIAXI trial. The PBAC also noted that the proportion of participants who experienced at least one TEAE in the SIPEXI trial was higher in the incobotulinumtoxinA arm (6–17 years age group, 18.2%) compared to the placebo arm (6–17 years age group, 15.3%) and the 2–5 years age group (14.3%). Overall, the PBAC considered that the claim of inferior safety of incobotulinumtoxinA versus placebo was reasonable.
- 7.9 The submission presented a cost-utility analysis to support the cost-effectiveness of incobotulinumtoxinA versus placebo, with the economic model reporting incremental cost-effectiveness ratios (ICERs) of \$25,000 to < \$35,000 per quality adjusted life year (QALY) gained for adults and \$35,000 to < \$45,000 per QALY gained for children and adolescents. The PBAC considered that the ICER values presented for the base case of the submission were acceptable. However, the PBAC noted that the economic evaluation was associated with a number of key uncertainties, as discussed in paragraphs 6.82 and 6.83 and 6.88 to 6.90. The PBAC considered that the assumption that the treatment effect would be maintained after repeated injections over a 5-year time horizon was inappropriate due to the lack of trial data beyond 64 weeks. The PBAC agreed with the ESC that, in this context, a time horizon of 2 years would be more appropriate. The PBAC advised that for incobotulinumtoxinA to be considered cost-effective the models should (i) incorporate a 2-year time horizon, and (ii) a price reduction so that the resultant ICERs do not exceed the base case values presented in the submission.
- 7.10 The PBAC noted that the DUSC considered the financial estimates presented in the submission to be underestimated primarily due the assumption that uptake would initially be slow in the Australian clinical setting, which may not be consistent with prescribing clinicians likely to be familiar with incobotulinumtoxinA from compassionate and off-label use. The PBAC also noted other uncertainties related to the financial estimates (Table 18); however, considered that, on balance, the incobotulinumtoxinA utilisation estimates provided in the submission were reasonable.

Outcome:

Deferred

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

The sponsor had no comment.