6.04 INCOBOTULINUMTOXINA, 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 (hereafter named Xeomin®) 100 units (U) for the treatment of moderate to severe spasticity of the upper limb and dynamic equinus foot deformity (common presentation of lower limb spasticity) due to spasticity in patients with cerebral palsy aged 2 years and older.

1.2 Listing was requested on the basis of a cost-minimisation approach vs botulinum toxin type A (Botox). 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	• Moderate to severe spasticity of the upper limb in cerebral palsy patients aged ≥2 years. • Dynamic equinus foot deformity due to spasticity in cerebral palsy patients aged ≥2 years.	
Intervention	IncobotulinumtoxinA, purified Botulinum toxin type A, free from complexing proteins (Xeomin®)	
Comparator	Botulinum toxin type A (Botox®)	
Outcomes	**Primary efficacy endpoints:** <u>Moderate to severe spasticity of the upper limb</u> • Change from baseline in Ashworth scale (AS) in the primary clinical target pattern, i.e. elbow flexors or wrist flexors • Investigator's Global Impression of Change Scale (GICS) <u>Dynamic equinus foot deformity due to spasticity</u> • Change from baseline in the AS score of plantar flexors • Investigator's GICS	**Primary safety endpoints**: <u>Moderate to severe spasticity of the upper limb</u> • Occurrence of treatment emergent adverse events (TEAEs) overall and per injection cycle <u>Dynamic equinus foot deformity due to spasticity</u> • Occurrence of TEAEs overall and per injection cycle
Clinical claim	• Xeomin is non-inferior to Botox for the treatment of moderate to severe upper limb spasticity in individuals with cerebral palsy aged ≥2 years. • Xeomin is non-inferior to Botox for the treatment of dynamic equinus foot deformity due to spasticity in individuals with cerebral palsy aged ≥2 years.	

Source: Source: Table 1.1.1, pp 1-2 of the submission.

2 Background

2.1 Xeomin is currently PBS-listed under Section 100 (Botulinum Toxin Program) for the treatment of blepharospasm, spasmodic torticollis and moderate-to-severe spasticity

of the upper limb following an acute event for patients aged 18 years or older. Xeomin is not PBS-listed for any indications in the paediatric population (aged 2 to 17 years).

Registration status

2.2 Xeomin was first TGA (Therapeutic Goods Administration) registered on 21 March 2014 for the treatment of cervical dystonia and blepharospasm in adults. Xeomin was TGA registered in November 2023 for the symptomatic treatment of paediatric spasticity of the lower and/or upper limb in children and adolescents (aged 2-17 years) and spasticity of the upper limb in adults (≥18 years).

2.3 The TGA indications for Xeomin for adults are for the treatment of:

- Cervical dystonia (spasmodic torticollis),
- Blepharospasm,
- Spasticity of the upper limb,
- Unilateral spasticity of the lower limb affecting the ankle joint
- Chronic sialorrhea due to neurological disorders,
- Upper facial lines:
  - Glabellar frown lines,
  - Lateral periorbital lines (crow's feet),
  - Horizontal forehead lines.

2.4 Xeomin was TGA registered for adults with unilateral spasticity of the lower limb affecting the ankle joint on 8 May 2025. The Economic Sub-Committee (ESC) noted that TGA registration for this indication was based on a double-blind, placebo-controlled Phase III clinical trial in adult patients with unilateral lower-limb spasticity and possessing equinus foot deformity caused by a stroke.

2.5 The TGA indications for Xeomin for children and adolescents aged 2 years to 17 years are for the symptomatic treatment of:

- Chronic sialorrhea due to neurological/neurodevelopmental disorders,
- Spasticity of the lower and/or upper limbs.

2.6 Xeomin is approved by the Food and Drug Administration for upper limb spasticity in children and adolescents aged 2-17 years, excluding cerebral palsy-related cases. The European Medicines Agency has approved it for adult upper limb spasticity only.

Previous PBAC consideration

2.7 The Pharmaceutical Benefits Advisory Committee (PBAC) has not previously considered Xeomin for the treatment of moderate-to-severe spasticity of the upper limb and dynamic equinus foot deformity due to spasticity in patients with cerebral palsy aged 2 years and older.

2.8 The PBAC previously recommended Xeomin for the treatment of blepharospasm (item 10994P), spasmodic torticollis or cervical dystonia (item 11005F), and moderate to severe spasticity of the upper limb/s following an acute event (item 12087E) in adults (≥18 years) (paragraph 7.1, IncobotulinumtoxinA (Xeomin), Public Summary Document (PSD), July 2014 PBAC Meeting; paragraph 6.1, Xeomin, PSD, November 2019 PBAC Meeting).

2.9 Table 2 presents the previous key PBAC positive recommendations of the three listed botulinum toxin preparations: incobotulinumtoxinA (Xeomin), botulinum toxin type A (Botox), and clostridium botulinum type A toxin-haemagglutinin complex (Dysport).

Table 2: List of recommended submissions of Xeomin, Botox, and Dysport

Date	Requested listing
List of previous Xeomin PBAC considerations	
July 2014 meeting	Spasmodic torticollis in patients 18 years or older
November 2019 meeting	Treatment of moderate to severe spasticity of the upper limb following an acute event in patients 18 years or older
List of previous Botox PBAC considerations for the requested indications	
December 1999 meeting	Treatment of dynamic equinus foot deformity due to spasticity in juvenile cerebral palsy patients 2 years of age and older [a]
November 2008	Treatment of moderate to severe spasticity of the upper limb(s) in cerebral palsy patients aged 2 years and over
November 2019	Treatment of moderate to severe spasticity of the upper limb following an acute event in patients 18 years or older
List of previous Dysport PBAC considerations for the requested indications	
December 2001	Treatment of dynamic equinus foot deformity due to spasticity in juvenile cerebral palsy patients 2 years of age and older [b]
July 2020	Treatment of moderate to severe focal spasticity of the upper limb in patients (2 to 17 years inclusive and 18 years or older) with cerebral palsy

Source: PSDs for each item from 2005 onwards; items prior to 2005 sourced from the PBAC Meeting Index and mentions in other PSDs.
PSD= Public Summary Document; PBAC= Pharmaceutical Benefits Advisory Committee.
[a] Source: Section 2, p1, Botox PSD, November 2005 PBAC meeting.
[b] Source: Section 2, p1, Dysport PSD, November 2007 PBAC meeting.

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

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
INCOBOTULINUMTOXINA					
IncobotulinumtoxinA 100 units injection, 1 vial	$1,098.67	4	4	0	Xeomin

Category / Program: Section 100 (Botulinum toxin program)
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (STREAMLINED)
Condition: Dynamic equinus foot deformity
Treatment Phase: Initial and continuing
Clinical criteria:
The condition must be due to spasticity; AND Patient must have cerebral palsy; AND Patient must be ambulant
Treatment criteria:
Must be treated by a neurologist; OR Must be treated by an orthopaedic surgeon; OR Must be treated by a paediatrician; OR Must be treated by a rehabilitation specialist
Population criteria:
Patient must be aged from 2 to 17 years inclusive.

Category / Program: Section 100 (Botulinum toxin program)
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (STREAMLINED)
Condition: Dynamic equinus foot deformity
Treatment Phase: Initial and continuing
Clinical criteria:
The condition must be due to spasticity, AND Patient must have cerebral palsy, AND Patient must be ambulant.
Treatment criteria:

Must be treated by a neurologist; OR Must be treated by an orthopaedic surgeon; OR Must be treated by a paediatrician; OR Must be treated by a rehabilitation specialist.
Population criteria:
Patient must be aged from 18 years or older.

Category / Program: Section 100 (Botulinum toxin program)
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (STREAMLINED)
Condition: Moderate to severe spasticity of the upper limb
Treatment Phase: Initial and continuing
Clinical criteria:
Patient must have cerebral palsy.
Treatment criteria:
Must be treated by a neurologist; OR Must be treated by an orthopaedic surgeon; OR Must be treated by a paediatrician; OR Must be treated by a rehabilitation specialist; OR Must be treated by a plastic surgeon.
Population criteria:
Patient must be aged from 2 to 17 years inclusive.

Category / Program: Section 100 (Botulinum toxin program)
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (STREAMLINED)
Condition: Moderate to severe spasticity of the upper limb
Treatment Phase: Initial and continuing
Clinical criteria:
Patient must have cerebral palsy.
Treatment criteria:
Must be treated by a neurologist; OR Must be treated by an orthopaedic surgeon; OR Must be treated by a paediatrician; OR

Must be treated by a rehabilitation specialist OR Must be treated by a plastic surgeon.
Population criteria:
Patient must be aged from 18 years or older.

3.1 The proposed approved ex-manufacturer price (AEMP) for the requested indications was $262.50, consistent with the Botox PBS listings for upper and lower (dynamic equinus foot deformity) limb spasticity in patients with cerebral palsy (aged ≥2 years). The requested listing, which is limited to patients with cerebral palsy, is narrower than the approved TGA indication, which does not limit use based on clinical criteria.

3.2 The submission requested listing Xeomin under Section 100 (Botulinum Toxin Program) as an Authority Required (STREAMLINED) restriction type. Previous PBS listings of Xeomin 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. The requested restriction type was reasonable.

3.3 The proposed listing for Xeomin is identical to that for Botox and Dysport in the target population (i.e., separate listing for paediatric (2-17 years) and adult (≥18 years) patients).

3.4 The proposed restriction for Xeomin does not include a caution for contraindications to treatment, whereas the Botox and Dysport listings do.

3.5 The proposed restrictions for Xeomin for dynamic equinus foot deformity and moderate to severe upper limb spasticity are consistent with the approved TGA indications for the paediatric population (2-17 years) and adults. For both lower and upper limb spasticity, the clinical evidence presented in the submission is limited to the paediatric population with cerebral palsy, with no supporting clinical data provided for adults.

3.6 The submission noted that the 2008 PBAC recommendation for Botox for upper limb spasticity was based on studies in patients under 18, but treatment was extended pragmatically to adults on the basis that cerebral palsy persists into adulthood and patients would likely have commenced treatment as children. In 2020, the PBAC applied a similar approach for Dysport, recommending use in adults despite the clinical trials being conducted in the paediatric population only (paragraph 7.6, Dysport, PSD, July 2020 PBAC meeting). The PBAC further considered that there was no clinical reason to expect reduced effectiveness in adults, provided fixed contractures had not developed. The current submission for Xeomin also presented clinical data from the paediatric population (aged 2-17 years) only; however, Xeomin is TGA-approved for upper limb spasticity in adults. As such, the requested restriction, which includes adults despite the supporting data being limited to children, is

consistent with the TGA indication and aligns with past PBAC precedent for Botox and Dysport. The Pre-Sub-Committee Response (PSCR) maintained that Xeomin should be treated the same as Botox and Dysport in this respect. The PSCR noted that the submission had provided a letter from the Rehabilitation Medicine Society of Australia and New Zealand provided a letter which supported use of Xeomin in the adult cerebral palsy population even in the absence of data in the adult population, as has been done with Dysport and Botox. The ESC considered that, provided fixed contractures had not developed, there would be no clinical reason to expect a lack of effectiveness in adults and noted that, given the nature of the therapy, treatment was unlikely to continue if no effect was observed.

3.7 Botox and Dysport were recommended for dynamic equinus foot deformity (lower limb) spasticity in December 1999 and December 2001 (Table 2), respectively. Although PSDs are not available publicly for this indication, the clinical studies presented in those submissions indicate that Botox and Dysport studies were conducted in paediatric populations. Botox was TGA-approved for use in adults and the TGA delegate had considered an application for Dysport for use in adults, at the time of PBAC recommendation. The current submission for Xeomin also presents paediatric data (age 2-17 years) only, and Xeomin is TGA-approved for lower limb spasticity in adults. Therefore, including adults in the proposed restriction is consistent with the current TGA registration status.

MSAC consideration

3.8 The sponsor submitted an MSAC application (application 1808) for the administration of Xeomin for the treatment of moderate to severe spasticity of the upper limb and dynamic equinus foot deformity in patients with cerebral palsy aged 2 years and older. Application 1808 was scheduled for consideration at the July MSAC meeting.

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

4 Population and disease

4.1 Cerebral palsy (CP) is a group of neurological disorders developing in early childhood, characterised by permanent impairments in movement, muscle coordination, posture, and balance due to injury or abnormal development within the brain.[1] Spasticity, a common clinical manifestation affecting approximately 70-90% of children with CP, involves increased muscle tone, stiffness, and hyperactive reflexes.[1] It significantly limits passive and active joint motion, leading to functional impairments

[1] Hallman-Cooper JL, Rocha Cabrero F. Cerebral Palsy. [Updated 2024 Feb 24]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538147/.

such as joint contractures, reduced mobility, impaired self-care, and pain, consequently diminishing the overall health-related quality of life.

4.2 Lower limb spasticity most commonly presents as dynamic pes equinus, occurring in up to 83% of children with bilateral CP.[1] This condition results from insufficient ankle dorsiflexion, causing toe-walking and often accompanied by knee and hip flexion or adduction deformities. Upper limb spasticity is observed in over 80% of children with CP, typically manifesting as increased flexor tone, compromising fine motor skills, hand positioning, and daily functional abilities. In terms of the spasticity causes, the known risk factors include low birth weight and prematurity.[1]

4.3 The clinical management algorithms in the submission were primarily based on Australian guidelines (Australian Therapeutic Guidelines, Royal Children's Hospital Melbourne and the Australasian Academy of Cerebral Palsy and Developmental Medicine). The guidelines cited the use of Botulinum toxin injections for upper and lower limb spasticity in children and adolescents with cerebral palsy.

4.4 As noted by the submission, apart from the potential substitution of Xeomin for Botox and Dysport, other aspects of the current treatment algorithms would not change. This was reasonable.

4.5 The submission adequately addressed the clinical management of upper and lower limb spasticity in patients with cerebral palsy in the paediatric population (2-17 years). The submission provided no discussion in Section 1 (the 'Context') of the relevance of the information provided to the proposed adult population (≥18 years).

4.6 *Clostridium botulinum* is a gram-positive, anaerobic, rod-shaped, spore-forming, motile bacterium capable of producing botulinum neurotoxin.[2] Xeomin is derived from this bacterium via fermentation and purified to remove associated complexing proteins, such as haemagglutinins and other non-toxic, non-haemagglutinating proteins, leaving only the purified neurotoxin.

4.7 The submission stated that Xeomin differs from other botulinum neurotoxins by containing only the purified 150 kilodalton (kD; 1 kD= 1000 grams/mol) neurotoxin, which may reduce immunogenic responses with repeated use[3]. This description is consistent with the Xeomin Product Information.

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

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[2] Tiwari A, Nagalli S. Clostridium botulinum Infection(Archived). 2024 Jul 2. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–. PMID: 31971722.

[3] Carr WW, Jain N & Sublett JW. Immunogenicity of Botulinum Toxin Formulations: Potential Therapeutic Implications. Advances in Therapy 2021; 38(10):5046-5064: 0.1007/s12325-021-01882-9

5 Comparator

5.1 The submission nominated Botox as the sole comparator. The main reasons provided for this nomination were as follows:

- Botox is PBS-listed for the treatment of moderate to severe upper limb spasticity and dynamic equinus deformity in patients aged ≥2 years with cerebral palsy and accounts for approximately 93% of the market in this population, based on PBS services data from 2020-2024.[4] Dysport accounts for only 7% (6% for 500 U and 1% for 300 U) over the same period and was therefore considered a less appropriate comparator.
- The TGA considered that a 1:1 therapeutic equivalence ratio between Botox and Xeomin was reasonable. This was based on the TGA approved indications for Xeomin (TGA Clinical Evaluation Report).
- The PBAC has previously advised that Botox, Dysport and Xeomin, should be treated as interchangeable on an individual patient basis under Section 101 (3BA) of the *National Health Act 1953* (paragraph 6.15, Xeomin, PSD, November 2019 PBAC meeting).

5.2 In the context of the cost-minimisation approach taken by the submission, under Section 101(3B) of the *National Health Act 1953*, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the PBAC is so satisfied, it must make a statement to this effect.

5.3 For the requested population, both Botox and Dysport may be considered alternative therapies because they could be replaced in practice. The PSCR considered Botox to be the only appropriate comparator for Xeomin noting Dysport was not interchangeable with Botox on a unit-to-unit basis, with Dysport requiring administration ratios between 2:1 and 9:1 to Botox. The PSCR also noted that Botox is a significant market leader for the botulinum toxin market accounting for 93% of the current market. The ESC noted that while there are slight differences between the formulations of Xeomin and Dysport, the mechanism of action and have the same place in the clinical management algorithm for upper and lower limb spasticity.

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

[4] Source: Calculated during the evaluation based on data presented in the submission in Section 4, Workbook 3, "Botulinum Toxin PBS Services".

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.1 The PBAC noted that no consumer comments were received for this item. The PBAC noted and welcomed the input from the Rehabilitation Medicine Society of Australia and New Zealand (RMSANZ) which was provided with the submission. The correspondence supported the listing of Xeomin on the PBS for adult and paediatric spasticity associated with cerebral palsy.

Clinical studies

6.2 There are no direct head-to-head double-blind randomised controlled trials (RCTs) comparing Xeomin and Botox for upper and lower limb spasticity in the paediatric or adult populations.

6.3 The submission was based on 2 pivotal phase 3 double-blind RCTs. The submission also presented data from one phase 3 open-label study and one prospective phase IV open-label study:

- TIM: A phase 3, prospective, multicentre, randomised, double-blind, parallel-group, dose-response trial evaluating the safety and efficacy of 3 doses of Xeomin (100 U, 200 U, 400 U) for the treatment of lower limb spasticity in children and adolescents (age 2-17 years) with cerebral palsy (N=311).
- XARA: A phase 3, prospective, multicentre, multi-national, randomised, double-blind, parallel-group, dose-response trial to investigate efficacy and safety of Xeomin (50 U, 150 U, 200 U) for the treatment of upper limb spasticity alone or combined upper and lower limb spasticity in children and adolescents (age 2-17 years) with cerebral palsy (N=350).
- TIMO: A phase 3, open-label, non-controlled, multicentre long-term study to investigate the safety and efficacy of Xeomin for the treatment of spasticity of the lower limb(s) or of combined spasticity of the upper and lower limb(s) in children and adolescents (age 2-17 years) with cerebral palsy (N=370).
- R-201212: A phase IV, prospective, open label, comparative, randomised, parallel-group, multicentre (3 study sites located in the Russian Federation) study to assess the clinical and neurophysiological efficacy as well as the safety of Xeomin vs Botox in children with spastic equinus or equinovarus foot deformation in children (aged 2-12 years) with cerebral palsy (N=64).

6.4 Details of the studies presented in the submission are provided in Table 3.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Xeomin®		
TIM	Phase 3, Prospective, multicentre, randomized, double-blind, parallel-group, dose-response study of three doses Xeomin (incobotulinumtoxinA, NT 201) for the treatment of lower limb spasticity in children and adolescents (age 2-17 years) with cerebral palsy. Heinen F, Kanovský P, Schroeder AS, Chambers HG, Dabrowski E, Geister TL, Hanschmann A, Martinez-Torres FJ, Pulte I, Banach M, Gaebler-Spira D. IncobotulinumtoxinA for the treatment of lower-limb spasticity in children and adolescents with cerebral palsy: A phase 3 study	CSR, November 2016 Journal of pediatric rehabilitation medicine. 2021 Jun 25;14(2):183-97
XARA	Phase 3, Prospective, multicentre, randomized, double-blind, parallel-group, dose-response study of three doses Xeomin (IncobotulinumtoxinA, NT 201) for the treatment of upper limb spasticity alone or combined upper and lower limb spasticity in children and adolescents (age 2-17 years) with cerebral palsy. Dabrowski E, Chambers HG, Gaebler-Spira D, Banach M, Kaňovský P, Dersch H, Althaus M, Geister TL, Heinen F. IncobotulinumtoxinA efficacy/safety in upper-limb spasticity in pediatric cerebral palsy: randomized controlled trial.	CSR, February 2019 Pediatric neurology. 2021 Oct 1;123:10-20.
TIMO	Phase 3, Open-label, non-controlled, multicentre long-term study to investigate the safety and efficacy of Xeomin (incobotulinumtoxinA, NT 201) for the treatment of spasticity of the lower limb(s) or of combined spasticity of upper and lower limb in children with adolescents (age 2-17 years) with cerebral palsy. Kaňovský P, Heinen F, Schroeder AS, Chambers HG, Dabrowski E, Geister TL, Hanschmann A, Martinez-Torres FJ, Pulte I, Banach M, Gaebler-Spira D. Safety and efficacy of repeat long-term incobotulinumtoxinA treatment for lower limb or combined upper/lower limb spasticity in children with cerebral palsy.	CSR, June 2017 Journal of pediatric rehabilitation medicine. 2022 Mar 29;15(1):113-27.
R-201212	Phase IV, multicentre, open, comparative randomized trial of clinical and neurophysiological efficacy and safety of Xeomin (botulinum toxin type A) vs. Botox (complex of botulinum toxin type A and hemagglutinin) in children with spastic equine and equinovarus foot deformation in paediatric (age 2-12 years) cerebral palsy. Kurenkov AL, Klochkova OA, Bursagova BI, Karimova HM, Kuzenkova LM, Mamedyarov AM, Namazova-Baranova LS, Agranovich OV, Agranovich AO, Soboleva OA, Khapaeva MM. Efficacy and safety of botulinum toxin type A (IncobotulinumtoxinA) in the treatment of patients with cerebral palsy.	CSR, November 2017 Zhurnal nevrologii i psikhiatrii imeni SS Korsakova. 2017 Jan 1;117(11):37-44. (Publication in Russian)
Botox®		
Flett 1999	Flett PJ, Stern LM, Waddy H, Connell TM, Seeger JD, Gibson SK. Botulinum toxin A versus fixed cast stretching for dynamic calf tightness in cerebral palsy.	Journal of paediatrics and child health. 1999 Feb;35(1):71-7.
Fehlings 2000	Fehlings D, Rang M, Glazier J, Steele C. An evaluation of botulinum-A toxin injections to improve upper extremity function in children with hemiplegic cerebral palsy.	The Journal of pediatrics. 2000 Sep 1;137(3):331-7.

Lowe 2006	Lowe K, Novak I, Cusick A. Low-dose/high-concentration localized botulinum toxin A improves upper limb movement and function in children with hemiplegic cerebral palsy.	Developmental medicine and child neurology. 2006 Mar;48(3):170-5.
Russo 2007	Russo RN, Crotty M, Miller MD, Murchland S, Flett P, Haan E. Upper-limb botulinum toxin A injection and occupational therapy in children with hemiplegic cerebral palsy identified from a population register: a single-blind, randomized, controlled trial.	Pediatrics. 2007 May 1;119(5):e1149-58.

Source: CSR= Clinical Study Reports; Tables 2.2.2 and 2.2.3, pp25-27 of the submission.

6.5 The key features of the Botox studies are summarised in Table 4.

Table 4: Key features of Botox studies used in cross-trial comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Botox vs. no intervention					
Flett 1999	20	R, SB (6 mths)	High	Age 2 to 8 years, CP and muscle spasticity of the lower extremity	MAS, GMFM scores, total PRS and GSS scores
Fehlings 2000	30	R, SB (6 mths)	High	Age 2.5 to 10 years; hand or arm hemiplegic CP	QUEST, MAS
Lowe 2006	42	R, SB (6 mths)	High	Age 2 to 8 years; hemiplegic CP, at least 2 on Ashworth scale	QUEST, GAS
Russo 2007	43	R, SB (6 mths)	High	Age 3 to 16 years hemiplegic CP, at least 2 on Modified Ashworth scale	MAS, Safety

Source: Table 2.6.1, p66 of the submission.
AS= Ashworth Scale; CP= Cerebral Palsy; GAS=goal attainment scale; GMFM= Gross Motor Function Measure; GSS= Global Scoring Scale; MAS= Modified Ashworth Scale; mths= months; OT= Occupational Therapy; PRS= Physician Rating Scale; QUEST=Quality of Upper Extremity Skills Test; R= randomised; SB= single blind; U= units.

6.6 Upper limb (UL) spasticity: The XARA study investigated the efficacy and safety of Xeomin in children and adolescents (age 2 - 17 years) with UL spasticity alone or with combined UL upper spasticity and lower limb spasticity due to cerebral palsy. The duration of study participation for subjects was 50 to 66 weeks, which consisted of a screening period of 2 weeks and 4 treatment cycles of 12 to 16 weeks each. In the main period, subjects were randomly allocated 2:1:1 to 3 parallel Xeomin dose groups, respectively: (i) high dose, 8 U/kg body weight (BW); (ii) mid dose, 6 U/kg BW; and (iii) low dose, 2 U/kg BW. In the open label extension (OLEX) phase, all subjects received Xeomin high dose (8 U/kg) with up to 3 treatment cycles.

6.7 Lower limb (LL) spasticity: The TIM trial evaluated the safety and efficacy of 3 doses of Xeomin for the treatment of LL spasticity in children and adolescents (age 2 - 17 years) with cerebral palsy. The duration of study participation for subjects was 26 to 74 weeks, which consisted of a screening period of 2 weeks followed by an observation period of 24 to 72 weeks, dependent on the timepoint of eligibility for re-injection. Eligible participants were randomised 1:1:2 to 3 parallel Xeomin dose groups, respectively: (i) low dose: 4 units/kilogram (U/kg) BW, maximum total dose 100 U; (ii)

mid dose: 12 U/kg BW, maximum total dose 300 U; and (iii) high dose: 16 U/kg BW, maximum total dose 400 U.

6.8 TIMO open label extension study: The TIMO trial investigated the safety and efficacy of Xeomin for the treatment of spasticity of the lower limb(s) or of combined spasticity of upper and lower limb in children and adolescents (age 2 - 17 years) with cerebral palsy. The study included subjects from the TIM pivotal trial (n = 124) and new recruits (n = 246). For subjects who completed the TIM trial, a total dose of 16 U/kg BW Xeomin (max 400 U) was injected (for the lower limb). For newly recruited subjects that had a clinical need for a lower limb or combined upper limb and lower limb spasticity treatment, a total dose of 16 to 20 U/kg BW Xeomin (max 500 U in subjects with combined lower limb and upper limb treatment and Gross Motor Function Classification System (GMFCS) levels I-III and max of 400 U in subjects with lower limb treatment and GMFCS levels I-V or combined lower limb and upper limb treatment and GMFCS levels IV-V) was injected at each injection visit, depending on chosen treatment combination. For the treatment of pes equinus (the most common presentation of lower limb spasticity), a fixed dose of 8 U/kg BW per treated side (max dose per pes equinus 200 U) was administered.

6.9 The only direct evidence comparing Xeomin and Botox came from Study R-201212, a phase IV, open-label, multi-centre (3 study sites located in the Russian Federation) study that assessed the efficacy and safety of Xeomin vs Botox in children (aged 2-12 years) with cerebral palsy with dynamic equinus foot deformity (lower limb). Participants received a single dose of Xeomin (n=32) or Botox (n=32), with 3 months of follow-up. Dosing was determined based on clinical presentation: children with unilateral pes equinus received 4 U/kg injected into the gastrocnemius muscle of the affected leg, while those with bilateral involvement received a total dose of 6-8 U/kg administered across both legs, up to a maximum of 300 U per treatment session.

Comparative effectiveness

6.10 The R-201212 study directly comparing Xeomin with Botox found a statistically significant improvement in the Modified Ashworth Scale (MAS; for the gastrocnemius muscle) at Day 30 compared to baseline in both the Xeomin group (1.8 ± 0.54, $p < 0.0001$) and the Botox group (1.6 ± 0.45, $p < 0.0001$), with no statistically significant differences between the two treatment groups ($p = 0.207$). However, only limited information was provided about this study, e.g., it was unclear whether participants had received prior Botox (noting the CSR was translated from Russian into English). Overall, due to the open-label design, lack of information available and relatively small sample size, the results of this study are considered to be supportive only, though they appear to demonstrate similar efficacy between Xeomin and Botox for lower limb spasticity in children aged 2-12 years (using a Xeomin dosing regimen of 4-8 U/kg).

6.11 The TGA Clinical Evaluation Report (CER) also considered the results of Study-R201212 as supportive evidence only due to the open-label design and small sample size for the treatment of lower limb spasticity in children aged 2-12 years (TGA CER). The TGA CER further stated that the therapeutic equivalence between Xeomin and Botox could not be demonstrated in the absence of a non-inferiority comparative trial and that the doses of Xeomin used in Study-R201212 are one-quarter to one-half the dose used in the phase III Xeomin clinical studies (TGA CER).

6.12 The submission did not conduct an indirect comparison between Xeomin and Botox (the primary comparator) or Dysport (which is also PBS-listed for this indication). Instead, it presented within-trial results from Xeomin trials (XARA and TIM) and Botox studies (Table 3), showing changes from baseline in Ashworth Scale or Modified Ashworth Scale scores, and, additionally for lower limb spasticity, changes in Gross Motor Function Measure (GMFM) scores from the TIM trial (for Xeomin) and a Botox study (Flett 1999). No attempt was made to adjust for differences between studies, such as participant characteristics, dosing protocols, or outcome measures, thereby limiting the validity of any implied comparison. The PSCR noted that a valid formal indirect comparison would require that all included studies are similar in factors which affect their result. The PSCR also noted that the general low quality of the primary comparator studies with lack of information in their published papers on study conduct and methodology, complicates the possibility of a formal indirect comparison. The ESC noted there are methods for adjusting for differential factors between trials.

6.13 The submission presented a side-by-side comparison of the Xeomin XARA trial and Botox studies to compare Xeomin and Botox for upper-limb spasticity due to cerebral palsy (Table 5).

Table 5: Xeomin vs Botox for upper-limb spasticity due to cerebral palsy, as presented in the submission

Xeomin	Baseline AS Mean (SD)	Change in AS score vs baseline, first measure [a] LSM (SE); (95% CI)	Change in AS score vs baseline, second measure [b] LSM (SE)
2 U/kg XARA	2.6 (0.52)	-0.93 (0.078); (-1.08; -0.78)	-0.4 (0.56)
6 U/kg XARA	2.6 (0.52)	-1.02 (0.082)	-0.4 (0.56)
8 U/kg XARA	2.7 (0.56)	-1.15 (0.056); (-1.26; -1.04)	-0.4 (0.63)
Botox	**Baseline MAS Mean (SD)**	**Change in MAS score vs baseline, first measure Mean (SD)**	**Change in MAS score vs baseline, second measure Mean (SD)**
Fehlings 2000			
No intervention	2.2 (0.59)	-0.26 (0.53)	-0.30 (0.49)
Botox	2.3 (0.75)	-0.34 (0.45)	-0.29 (0.41)
Lowe 2006			
No intervention	2.2 (0.1)	-0.03 (NR)	-0.15 (NR)
Botox	2.4 (0.1)	-1.1 (NR)	-0.8 (NR)
Russo 2007			
No intervention	2 (NR)	NR	2.0 (NR)
Botox	2 (NR)	NR	-1.0 (NR)

Source: Table 2.6.4, p67 of the submission.
AS= Ashworth scale; GMFM= gross motor function measure; kg= kilogram; LSM= least squares mean; MAS= modified Ashworth scale; NR= not reported; SD= standard deviation; U= unit.
[a] First measure= four weeks for Xeomin study, one month for Botox.
[b] Second measure= 14 weeks for Xeomin study, 3 months for Botox.

6.14 The naïve comparisons presented in Table 5 showed changes in spasticity scores between Xeomin (XARA trial) and Botox (from three published studies) using the AS and MAS, respectively. In the XARA trial, Xeomin showed dose-dependent reductions in AS scores at Week 4, with least squares mean (LSM) changes ranging from -0.93 (2 U/kg) to -1.15 (8 U/kg). The second measure at 14 weeks across all dose groups showed a consistent change of -0.4. In contrast, Botox studies showed variable results. In Fehlings (2000), Botox reduced MAS scores by -0.34, compared to -0.26 in the no-intervention group. Lowe (2006) reported a larger effect with Botox (-1.1 and -0.8 for first and second measures), while Russo (2007) showed a -1.0 change in the second MAS measure, although some data were not reported. Overall, Xeomin demonstrated consistent reductions in spasticity, while Botox's effectiveness varied across studies, with some comparator (no intervention) arms also showing modest improvements. However, differences in scales (AS vs MAS), study design (double vs single blind), and data completeness limit such comparisons.

6.15 Given the presentation of the naïve comparisons by the submission was limited, Table 6 was constructed during the evaluation, including results from the XARA trial for Xeomin and results from the Dysport PSD (July 2020 PBAC meeting), which included a formal indirect comparison of Dysport and Botox using MAS outcomes at Week 6.

Table 6: (A) Results for Xeomin for AS in the UL main clinical target pattern (flexed elbow or flexed wrists) at week 4; and (B) results of the indirect comparison Dysport and Botox for MAS PTMG at week 6

	Change from baseline in AS (LSM)			Difference in change from baseline (95% CI)
Week 4	**Xeomin**	**Common reference no intervention**		
2 U/kg XARA	N=85 -0.93 (-1.08, -0.78)	-	-	**-**
6 U/kg XARA	N=87 -1.02 (-1.19, -0.86)			
8 U/kg XARA	N=173 -1.15 (-1.26, -1.04)	-	-	**-**
	Change from baseline in MAS PTMG (LSM[a])			**Difference in change from baseline (95% CI)**
Week 6	**Dysport**	**Common reference no intervention [b]**	**Botox**	
8 U/kg Study 153	N=69 -2.0	N=69 -1.6	-	**-0.40 (-0.75, -0.05)**
16 U/kg Study 153	N=70 -2.3	N=69 -1.6	-	**-0.70 (-1.03, -0.37)**
Pooled Dysport fixed effects (I^2=32.3%; p=0.22)				**-0.56 (-0.80, -0.32)**
6 U/kg Fehlings 2018	-	N=79 -1.1	N=77 -1.9	**-0.60 (-0.90, 0.30)**
3 U/kg Fehlings 2018	-	N=79 -1.1	N=78 -1.9	**-0.72 (-0.98, -0.46)**
Pooled Botox fixed effects (I^2=0%; p=0.55)				**-0.67 (-0.87, -0.47)**
Indirect pooled Dysport vs pooled Botox (95% CI)				0.11 (-0.20, 0.42)
Indirect Dysport 8 U/kg vs pooled Botox (95% CI)				0.27 (-0.13, 0.67)
Indirect Dysport 16 U/kg vs pooled Botox (95% CI)				-0.03 (-0.42, 0.36)

Source: Table 6, Dysport Public Summary Document, July 2020 PBAC Meeting; Tables 2.5.3, p56 of the submission; Table 34, XARA CSR.

CI=confidence interval; CSR=clinical summary report; LSM=least square mean; MAS=Modified Ashworth Scale; NR=not reported; PTMG=primary target muscle group; UL = upper limb, **bold**=statistically significant; light blue shading indicates results previously seen by the PBAC.

[a] Both the submission and the Study 153 CSR provided only least square mean change from baseline values, there were no standard deviations or standard errors provided.

[b] In Study 153, the 2 U/kg Dysport arm of the trial was used as the 'no intervention' arm.

6.16 A comparison of results from the XARA trial of Xeomin and the published studies of Botox and Dysport in Table 6 showed improvements from baseline in spasticity scores. Dysport demonstrated dose-dependent reductions (-2.0 at 8 U/kg and -2.3 at 16 U/kg), while Botox consistently showed a reduction of -1.6. Indirect comparisons between Dysport and Botox showed overlapping confidence intervals, with no statistically significant differences in most pairwise comparisons. In contrast, Xeomin demonstrated LSM reductions from baseline in AS scores ranging from -0.93 to -1.15 at Week 4. While these results suggest that Xeomin and Botox (also Dysport) reduced spasticity, the methodological limitation of this unanchored, unadjusted comparison restricts meaningful comparisons between the treatments due to differences in outcome measures (AS vs MAS), dosages, time points (Weeks 4 vs 6), and participant characteristics.

6.17 In particular, there were differences in the outcome measures used – the key studies for Botox and Dysport used the MAS, while the XARA used the AS. Both are rating scales that measure abnormality in tone or the resistance to passive movements, however, the AS is a 5-point scale with a grade score of 0, 1, 2, 3, or 4, while the MAS is a 6-point scale with an additional grade of 1+ (plus minor changes in the definitions of each score). The PSCR claimed the PBAC previously considered AS and MAS scores equivalent when evaluating outcomes between Dysport and Botox as part of its consideration of the July 2020 Dysport submission for upper-limp cerebral palsy spasticity. The ESC noted the July 2020 Dysport PSD does not explicitly state that the PBAC considered AS and MAS scores to be equivalent, only that both scales have been used in numerous PBAC submissions for lower and upper limb spasticity (paragraph 6.12, Dysport PSD, July 2020 PBAC meeting).

6.18 Previously, for the indirect comparisons between the pivotal Dysport trial and five Botox trials for the upper limb spasticity in patients with cerebral palsy, the PBAC noted that the indirect comparisons were limited due to a number of issues, including small participant numbers in most of the Botox trials, heterogeneity in many of the comparisons, and wide confidence intervals and/or few or no events for many of the safety comparisons (paragraph 7.7, Dysport PSD, July 2020 PBAC meeting). However, overall, the PBAC considered that the evidence suggested that Dysport was likely to be non-inferior to Botox in terms of efficacy and safety (paragraph 7.7, Dysport PSD, July 2020 PBAC meeting).

6.19 The TGA evaluator stated that, for UL spasticity, the high dose Xeomin group achieved a statistically significant and greater mean change from baseline in AS score compared to the low dose group (TGA CER). The step 4 analysis of the primary efficacy variable did not demonstrate statistical separation between the mid-dose vs low-dose groups, although the magnitude of the treatment effect in both groups was clinically meaningful (LSM changes were -1.02 and -0.96, respectively) (TGA CER). No major differences were observed across dose groups overall.

6.20 The submission presented a side-by-side comparison of the Xeomin TIM trial and a Botox study (Flett 1999) to compare Xeomin and Botox for lower-limb spasticity due to cerebral palsy (Table 7).

Table 7: Xeomin vs Botox for lower-limb spasticity due to cerebral palsy, as presented in the submission

Xeomin	Baseline AS Mean (SD)	Change in AS score (primary body side) at 8 weeks vs baseline LSM (SE); (95% CI)
4 U/kg TIM	2.8 (0.5)	-0.69 (0.080); (-0.85; -0.53)
12 U/kg TIM	2.7 (0.5)	-0.74 (0.088); (-0.91; -0.56)
16 U/kg TIM	2.7 (0.6)	-0.62 (0.059); (-0.73; -0.50)
Botox	**Baseline MAS: Mean (SD)**	**Change in MAS score (primary body side) at 8 weeks vs baseline: Mean**
4 to 8 U/kg Flett 1999	Assessed by a physio: 2.41 (0.65) Assessed by a doctor: 2.69 (0.75)	Assessed by a physio: -1.01 Assessed by a doctor: -1.29

Source: Table 2.6.3, p66 of the submission.
AS= Ashworth scale; GMFM= gross motor function measure; kg= kilogram; LSM= least squares mean; MAS= modified Ashworth scale; SD= standard deviation; U= unit.

6.21 A comparison of results from the TIM trial for Xeomin and the Botox study (Flett 1999) in Table 7 showed that both treatments demonstrated improvements from baseline in spasticity scores at 8 weeks. In the TIM trial, Xeomin produced LSM changes from baseline in AS scores ranging from -0.62 to -0.74 across the 4 U/kg to 16 U/kg dose groups. The Botox study reported changes from baseline in MAS scores of -1.01 (physiotherapist assessment) and -1.29 (doctor assessment) for doses of 4 to 8 U/kg. While both treatments showed reductions in spasticity, the results for Botox indicated a larger numerical improvement. However, as stated above for UL spasticity, differences in outcome measures (AS vs MAS), assessment methods (assessor variability), study design (single blind vs double blind) and other differences limit the ability to compare treatment effects between Xeomin and Botox.

6.22 The submission stated that the TIM trial showed a positive and clinically meaningful treatment response in all treatment groups at Week 4 after injection in pes equinus, as demonstrated by the AS and GICS-PF assessment. The results also indicated a favourable safety and tolerability profile at doses of up to 16 U/kg (maximum 400 U) for participants in all Gross Motor Function Classification System severity groups.

6.23 The TGA evaluator stated that subjects in both high and low dose Xeomin groups achieved improvement in the TIM trial (TGA CER). However, the change from baseline in the mid-dose group difference was not statistically significant. In terms of co-primary and secondary outcomes, overall, subjects in both treatment arms experienced an improvement in their spasticity. However, treatment difference between dose groups or injection cycles did not achieve statistical significance (TGA CER).

6.24 The submission stated that the phase III TIMO clinical trial shows that in a paediatric population with CP, treatment with Xeomin offered significant and consistent improvement in muscle tone and motor function for children with CP spasticity in lower and/or upper limb(s). The TGA evaluator noted a change from baseline in AS

score of plantar flexors showed slight improvements from baseline in AS scores from cycle to cycle in both left and right flexors (TGA CER). The submission stated that the long-term efficacy of up to 4 injections of Xeomin was clearly and consistently demonstrated in TIMO and corresponded well to the results of the lead-in study. This was reasonable.

6.25 Overall, the TGA evaluator stated that the magnitude of benefit was comparable between the Xeomin studies over the dose range of 4 to 16 U/kg for both upper limb, lower limb and combined upper limb and lower limb spasticity (TGA CER).

6.26 The PBAC previously considered that despite the lack of clinical trials in aetiologies other than stroke, the request to extend the listing of botulinum toxins to include moderate to severe spasticity of the lower limb following acute events was reasonable and biologically plausible (paragraph 5.2, Botox PSD, March 2019 PBAC meeting; paragraph 7.2, Dysport PSD, July 2019 PBAC meeting). In addition, at its July 2014 meeting when Xeomin was recommended for post-stroke upper limb spasticity on the basis of a cost-minimisation approach with Botox, the PBAC considered that both agents would likely have similar clinical effects as they are analogues of each other (paragraph 6.17, Xeomin PSD, July 2014 PBAC meeting).

Comparative harms

6.27 The submission did not present any comparison between the safety of Xeomin and Botox.

6.28 The TGA evaluator stated that most of the safety-related events were previously reported in studies with botulinum products. For the Xeomin studies, the TGA evaluator noted that the highest proportion of subjects that reported treatment emergent adverse events (TEAEs) was in the Infections and Infestations System Organ Class category, driven by nasopharyngitis, across the controlled phase III studies (TGA CER). No serious events related to distant spread of toxin were reported. There were generally no meaningful dose-related trends or patterns of TEAEs related to the number of injection cycles (TGA CER). However, long term safety data for the use of Xeomin in the target patient population is limited (TGA CER).

Benefits/harms

6.29 A benefits and harms table is not presented as the submission made a claim of non-inferiority.

Clinical claim

6.30 The submission described Xeomin as non-inferior in terms of comparative effectiveness and safety compared to Botox. The evaluation considered that the available evidence did not support this claim because of the lack of a direct and

indirect comparison. The comparisons presented were limited to cross-trial comparisons of changes from baseline without appropriate adjustment for key differences in outcome measures (e.g., use of AS vs MAS), dosing regimens, time points for assessment, and participant characteristics. This approach does not meet the methodological standards for an indirect comparison as outlined in the PBAC guidelines, and the non-inferiority claim should therefore be interpreted with caution. For example,

- Time points for assessment: The primary efficacy outcomes in the Xeomin trials were assessed at specific time points (e.g., Week 4), while the Botox studies assessed outcomes at different time points (e.g., Week 6 or Week 12), making comparisons of change from baseline unreliable without adjustment.
- Participant characteristics: Differences between studies included variability in participant age distribution, severity of spasticity at baseline (as measured by AS/MAS scores), prior exposure to botulinum toxin treatment (toxin-naïve vs pre-treated participants), and functional status (e.g., GMFCS level or ambulant vs non-ambulant participants).

6.31 In addition, the safety and efficacy data presented in the submission were limited to the paediatric population (aged 2-17 years; mean age of Xeomin trial participants was < 10 years), with no clinical evidence provided to support the use of Xeomin in adults.

6.32 Whilst recognising the uncertainties associated with the unadjusted comparisons, the PBAC considered that overall, the claim of non-inferior comparative effectiveness was reasonable. The PBAC recalled it previously considered Xeomin and Botox would likely have similar effects as they are analogues of each other (paragraph 6.17, Xeomin PSD, July 2014 PBAC meeting).

6.33 The PBAC considered the claim of comparable safety to Botox was reasonable.

Economic analysis

6.34 The submission presented a cost-minimisation approach comparing Xeomin to Botox based on cross-trial comparisons.

6.35 Table 8 describes the key components and assumptions of the cost-minimisation approach.

Table 8: Key components and assumptions of the cost-minimisation approach

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on the evidence presented in Section 2 (the 'Clinical evaluation'), effectiveness was assumed to be: Xeomin is non-inferior to Botox in patients 2 years and older with upper or lower limb spasticity due to cerebral palsy. The evaluation considered that the submission did not establish non-inferiority of Xeomin compared to Botox in terms of effectiveness, and non-inferiority relative to Dysport was also not attempted.
Therapeutic claim: safety	Based on the evidence presented in Section 2, safety was assumed to be: Xeomin is non-inferior to Botox in patients 2 years and older with upper or lower limb spasticity due to cerebral palsy. The evaluation considered that the submission did not establish non-inferiority of Xeomin compared to Botox in terms of safety, and non-inferiority relative to Dysport was also not attempted.
Evidence base	Cross-trial comparison using randomised controlled trials.
Equi-effective doses	Xeomin 400 U is equivalent to Botox 400 U (i.e. Xeomin 1 U = Botox 1 U). Taking the submission's proposed equi-effective dose, Xeomin 400 U would be equivalent to Dysport 1000 U (i.e. Xeomin 1 U = Dysport 2.5 U) based on the established equi-effective dose of Botox 400 U = Dysport 1000 U (paragraph 7.10, Dysport, PSD, July 2020 PBAC Meeting).
Direct medicine costs	• The AEMP and DPMQ for Xeomin were considered equivalent to those of Botox. • AEMP for Botox 100 U (PBS items:10998W and 10999X): $262.50. • AEMP for Dysport 300 U (PBS items: 10981Y and 12214W) = $228.39; Dysport 500 U (PBS items: 11006G and 12178Y) = $407.37. • DPMQ for Botox (PBS items:10998W and 10999X) = $1,098.67[a]. • DPMQs Dysport 300 U (PBS items: 10981Y and 12214W) = $958.79; Dysport 500 U (PBS items: 11006G and 12178Y) = $855.99. • Maximum dosage per patient per treatment cycle for chronic or continuing therapy. • Costs of monitoring or managing adverse events = none considered.
Other costs or cost offsets	Not considered; only drug cost was presented in the analysis. This was reasonable.

Source: Table 3.1.1, p78 of the submission; AEMPs and DPMQs as of 1 April 2025 based on www.pbs.gov.au/industry/pricing/ex-manufacturer-price/2025/ex-manufacturer-prices-non-efc-2025-04-01.XLSX; Table 4.2.3, p82 of the submission.
AEMP = Approved ex-manufacturer price; DPMQ = Dispensed price for maximum quantity; PBS = Pharmaceutical Benefits Schedule; U = Units.
[a] In the submission, the cost per patient per treatment cycle of Xeomin was estimated to be equivalent to that of Botox (at published DPMQ).

6.36 The proposed equi-effective doses were estimated as:

- Xeomin 1 U = Botox 1 U.
- Xeomin 1 U = Dysport 2.5 U.

6.37 The relativity for Xeomin and Botox was consistent with previous PBAC recommendations for Xeomin and Botox. The PBAC previously considered that Xeomin is non-inferior to Botox in terms of efficacy and safety for treating cervical dystonia, blepharospasm, and post-stroke upper limb spasticity at a 1:1 dose ratio

(paragraph 7.7-7.8, Xeomin, PSD, July 2014 PBAC Meeting). Additionally, the TGA evaluator noted that, at face value, the assumed 1:1 therapeutic equivalence ratio between Botox and Xeomin was reasonable for the proposed spasticity indications (TGA CER).

6.38 When estimating PBS usage and financial implications, the submission also presented equi-effective doses for Xeomin compared to Dysport, which was 1:2.5. In the July 2020 PBAC submission for the listing of Dysport for the treatment of moderate to severe focal spasticity of the upper limb in patients with cerebral palsy in patients aged 2 years and older, the PBAC considered that the maximum quantity of Dysport would be 1000 U, and the maximum quantity of Botox would be 400 U, resulting in an equi-effective dose of Dysport 2.5 U = Botox 1 U (paragraph 7.10, Botox, PSD, July 2020 PBAC Meeting). Table 9 presents dose relativities for botulinum toxin treatments recommended by the PBAC.

Table 9: Equi-effective doses and dose relativities of botulinum toxins for spasticity indications

	PBAC meeting	Equi-effective doses	Dose relativities	Medical condition	Source
Botox vs Dysport	July 2008	Botox 229 U per treatment course = Dysport 989 U per treatment course	1:4.3	Moderate to severe spasticity of the lower limb in ambulatory adults following a stroke.	Botox PSD July 2008
Botox vs Xeomin	July 2014	Xeomin 229 U (over approx. 87 days) = Botox 229 U (over approx. 87 days)	1:1	Post-stroke upper limb spasticity.	Botox PSD July 2014
Xeomin vs Dysport	November 2019	Xeomin 400 U = Dysport 1500 U	1:3.75	Moderate to severe focal spasticity of the upper limb following a stroke to also include spasticity following acute events other than stroke	Xeomin PSD November 2019
Botox vs Dysport	July 2020	Botox 400 U = Dysport 1000 U	1:2.5	Moderate to severe focal spasticity of the upper limb in patients with cerebral palsy in patients aged 2 years and older.	Dysport PSD July 2020
Xeomin vs Botox	This submission	Xeomin 400 U = Botox 400 U	1:1	Moderate to severe upper limb spasticity and dynamic equinus foot deformity (lower limb) spasticity in patients with cerebral palsy aged 2 years and older.	Proposed by the submission
Xeomin vs Dysport	This submission	Xeomin 400 U = Dysport 1000 U[a]	1:2.5		Used in financial estimates

Source: Table 4.2.4, p83 of the submission; Table 3 of Xeomin, PSD, November 2019 PBAC Meeting; paragraph 7.10, Dysport, PSD, July 2020 PBAC Meeting; Paragraph 1, Botox, PSD, July 2008 PBAC Meeting; Paragraph 1.1, Xeomin, PSD, July 2014 PBAC Meeting; Paragraph 1.1, Xeomin, PSD, November 2019 PBAC Meeting; Paragraph 1.1, Dysport, PSD, July 2020 PBAC Meeting.

[a] Added during the evaluation.

PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PSD = Public Summary Document.

6.39 The submission stated that Xeomin does not require additional resources beyond those used to treat patients with Botox. This was reasonable. At the proposed equi-

effective doses, the listing of Xeomin is unlikely to have a financial impact on the PBS and MBS due to cost offsets from an equivalent decrease in the number of items processed for Botox. The PBAC previously recommended listing Xeomin for cervical dystonia, blepharospasm, and post-stroke upper limb spasticity based on cost-minimisation analyses compared to Botox, requiring no additional resources beyond those used for Botox treatment (para. 6.36, Xeomin, PSD, July 2014 PBAC Meeting).

6.40 The submission stated that there are no differences in the costs of monitoring or managing adverse events associated with the therapies. Without robust comparative safety evidence, it is uncertain whether differences between Xeomin and the comparator therapies (Botox or Dysport) in terms of adverse event profiles could lead to meaningful differences in costs associated with managing or monitoring adverse events.

6.41 Table 10 presents the results of the cost-minimisation approach (CMA). The submission stated that using the maximum dispensed quantity for Xeomin and Dysport therapies, three packs were required per year per patient, and the PBS pricing proposed for Xeomin for these requested indications was equivalent to the cost of Botox treatment and would not affect the prices of the currently listed Xeomin items. Accordingly, the submission conducted the CMA using the published DPMQ for Botox (i.e. $1,098.67). The CMA was conducted using AEMPs during the evaluation.

Table 10: Results of the cost-minimisation approach

Component	Xeomin	Botox	Dysport 300 U[d]	Dysport 500 U[d]
PBS items	–	10998W, 10999X	10981Y, 12214W	11006G, 12178Y
Units per vial	100 U	100 U	300 U	500 U
Equi-effective dose vs Xeomin[d]	-	1:1	1:2.5	1:2.5
Total dose per cycle[a,d]	400 U	400 U	1000 U	1000 U
Number of vials per cycle[b,d]	4	4	3.33	2
DPMQ	$1,098.67	$1,098.67	$958.79	$855.99
Cost per vial (AEMP)[d]	$262.50	$262.50	$228.39	$407.37
Cost per cycle (AEMP)[c,d]	$1,050.00	$1,050.00	$761.30	$814.74
Cost-minimisation of Xeomin to Dysport (additional cost)[d]	-		$288.70	$235.26

Source: Tables 36, p79 of the submission; Table 4.2.2, p82 of the submission, Ex-manufacturer prices as of 1 April 2025 based on https://www.pbs.gov.au/industry/pricing/ex-manufacturer-price/2025/ex-manufacturer-prices-non-efc-2025-04-01.XLSX.
AEMP = Approved ex-manufacturer price; DPMQ = Dispensed price for maximum quantity.
[a] Approximate cycle length for Xeomin and Botox = 12 Weeks; Dysport = 16 Weeks.
[b] Total dose per cycle divided by units per vial. The total dose per cycle for Dysport 300 U and 500 U was based on the PBAC's previous consideration that the maximum quantity of Dysport would be 1000 U and that of Botox would be 400 U (paragraph 7.10, Dysport, PSD, July 2020 PBAC Meeting).
[c] Cost per vial (AEMP) * number of vials per cycle.
[d] Added during the evaluation.

6.42 The CMA comparing Xeomin and Dysport 300 U and 500 U conducted during the evaluation resulted in additional costs relative to Dysport 300 U ($288.70) and Dysport 500 U ($235.26) per cycle.

6.43 The ESC noted that the submission did not present clinical evidence to justify a higher cost for Xeomin compared to Dysport. Consistent with Section 101(3B) of the *National Health Act 1953*, if a medicine is more costly than an alternative therapy, the Committee must be satisfied that it provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect. The pre-PBAC response proposed an average weighted price for Xeomin based on the utilisation of Botox and Dysport. The pre-PBAC response proposed that the price for Xeomin be based on a 90:10 split between Botox and Dysport. The pre-PBAC response considered this was a conservative approach noting the market split of 93% Botox and 7% Dysport based on PBS services for the requested indications over the last calendar year.

Drug cost/patient/year

6.44 The financial model assumed 3 scripts per year for Xeomin, costing $3,296 (based on DPMQ of $1,098.67) per patient annually, but this likely underestimated the treatment cost. The Product Information for Xeomin indicated that the minimum time between treatments is 12 weeks, equivalent to 4.35 scripts per year (p4 of the TGA PI for Xeomin). Consequently, the annual cost of treating moderate to severe upper and

lower limb spasticity in patients aged 2 years and older with cerebral palsy using Xeomin was estimated to be $4,777.25 per patient.

6.45 Assuming a dosing frequency of every 16 weeks for Dysport, the estimated annual cost per patient was $3,126.77 for Dysport 300 U and $2,791.52 for Dysport 500 U.

Estimated PBS usage & financial implications

6.46 This submission was not considered by DUSC.

6.47 The submission used a market share approach to estimate the utilisation and financial implications associated with the PBS listing of Xeomin for treating moderate to severe upper limb and lower limb spasticity in patients with cerebral palsy. This approach was chosen because the botulinum toxin market is well-established and mature, particularly for treating upper and lower limb spasticity in children with cerebral palsy. The analysis included the substitution of Botox and Dysport. This was reasonable.

6.48 Table 11 presents the key inputs used in the financial estimates.

Table 11: Key inputs for financial estimates

Data	Value	Source	Comment
Eligible population			
Current botulinum toxin market size (number of PBS services)	4,724; Botox: 93%, Dysport: 7%	PBS usage data for Botox and Dysport items (2024).	This was reasonable.
Annual growth in botulinum toxin scripts	4.1%	PBS usage data (2020-2024); Averaged growth rates.	The assumed constant growth rate of 4.1% per year from 2025 to 2030 was uncertain. Between 2023 and 2024, the combined growth rate for Botox and Dysport was 10%.
Treatment utilisation			
Xeomin substitution of Botox and Dysport	Y1: [redacted]% Y2: [redacted]% Y3: [redacted]% Y4: [redacted]% Y5: [redacted]% Y6: [redacted]%	Submission projections.	Likely underestimated. Uptake in initial years may be higher as specialists are already familiar with Xeomin. In its advice to the PBAC regarding Xeomin for treating chronic sialorrhea, the DUSC considered that clinicians would not require training as they would be familiar with its use off-label, particularly for patients in palliative care (DUSC advice to the PBAC for chronic sialorrhea). Additionally, no evidence was provided regarding how these uptake rates were estimated, nor was a rationale given for the varying uptake rates across the first 6 years of listing. The submission included a sensitivity analysis that varied uptake rates by ±20%.
Script equivalence			
Script equivalence (Xeomin vs Botox)	1:1	Xeomin and Botox are equivalent on a unit-per-patient basis.	This was reasonable. The PBAC previously considered that Xeomin is non-inferior to Botox in terms of efficacy and safety for treating cervical dystonia, blepharospasm, and post-stroke upper limb spasticity at a 1:1 dose ratio (paragraph 7.7-7.8, Xeomin, PSD, July 2014 PBAC Meeting). Additionally, the TGA evaluator noted that, at face value, the assumed 1:1 therapeutic equivalence ratio between Botox and Xeomin was reasonable for the proposed spasticity indications (TGA CER). However, there is no indirect treatment comparison between the 2 treatments and no non-inferiority analysis.
Script equivalence (Xeomin vs Dysport)	1:2.5	The PBAC listed Dysport against Botox at a 2.5:1 ratio.	This was reasonable. In the July 2020 PBAC submission for the listing of Dysport for the treatment of moderate to severe focal spasticity of the upper limb in patients with cerebral palsy in patients aged 2 years and older, the PBAC considered that the maximum quantity of Dysport

Data	Value	Source	Comment
			would be 1000 U, and the maximum quantity of Botox would be 400 U, resulting in an equi-effective dose of Dysport 2.5 U = Botox 1 U (paragraph 7.10, Botox, PSD, July 2020 PBAC Meeting).
Costs			
Maximum quantity (packs and units)	4 Xeomin, Botox, and Dysport 300 U and 2 for Dysport 500 U	Based on maximum quantities for PBS items 10998W, 10999X, 10981Y, 12214W, 11006G and 12178Y.Botox	This was reasonable.
Xeomin	$1,098.67	Based on DPMQ for Botox.	This was reasonable.
Botox	$1,098.67	PBS items 10998W and 10999X.	DPMQ verified as correct at time of evaluation.
Dysport (300 U)	$958.79	PBS items 10981Y and 12214W.	DPMQ verified as correct at time of evaluation.
Dysport (500 U)	$855.99	PBS items 11006G and 12178Y.	DPMQ verified as correct at time of evaluation.
Patient co-payment	$15.19 (PBS) $3.85 (RPBS)	Assumed based on PBS usage data for Botox and Dysport (2024) and PBS/RPBS co-payments ($31.60 for the general population and $7.70 for concession card holders).	This was reasonable.
MBS costs (injection fee)	MBS items 18354 and 18361: $113.80	MBS benefit of 80% (Scheduled fee: $142.25). Applied only on Dysport but not Botox (as assumed the same for Botox)).	This was appropriate.

Source: Table 4.2.2, p82; Table 4.2.3, p82; Table 4.2.4, p83; Table 4.3.2, p85 of the submission; Sheet "2e. Scripts – market", Workbook 4; p81 of the submission

DPMQ = dispensed price for maximum quantity; DUSC = Drug Utilisation Sub Committee; MSAC = Medical Services Advisory Committee; MBS = Medicare Benefits Schedule; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PSD = Public Summary Document; RPBS = Repatriation Pharmaceutical Benefits Scheme TGA CER = Therapeutic Goods Administration Clinical Evaluation Report.

6.49 The submission estimated the growth rate of the botulinum toxin market using PBS service data from 2020 to 2024 and projected a steady annual growth rate of 4.1%. This annual growth rate was an average of the growth rates from 2020 to 2024. The assumed constant growth rate of 4.1% per year from 2025 to 2030 was uncertain. Between 2023 and 2024, the combined growth rate for Botox and Dysport was 10%.

6.50 The submission assumed that [redacted]% of patients on Botox or Dysport would switch to Xeomin in Year 1, increasing to [redacted]% in Year 6. The submission stated that the uptake

rates for Xeomin were "based on their own general commercial experience". No evidence was provided regarding how these uptake rates were estimated, nor was a rationale given for the varying uptake rates across the first 6 years of listing.

6.51 The submission further stated that the substitution rate was expected to be extremely low in the first year of listing as Xeomin established itself on the market as a treatment for these conditions but would gradually increase over the subsequent years. Uptake in initial years may be higher as specialists are already familiar with Xeomin. In its advice to the PBAC regarding Xeomin for treating chronic sialorrhea, the DUSC considered that clinicians would not require training as they would be familiar with its use off-label, particularly for patients in palliative care (DUSC advice to the PBAC for chronic sialorrhea). The PSCR considered the uptake is expected to be low in the first years of listing due to Botox already capturing over 90% of the total market and the listing of Xeomin is not expected to grow the market by introducing new patients.

6.52 The total number of Xeomin scripts projected to be dispensed over 6 years (from < 500 in Year 1 to 500 to < 5,000 in Year 6) was estimated to be slightly lower than the corresponding reduction in PBS services for Botox and Dysport resulting from the listing of Xeomin (from - < 500 in Year 1 to -500 to < 5,000 in Year 6). This was reasonable. The slight decrease in total Xeomin prescriptions was due to the substitution of Dysport with Xeomin at a 2.5:1 ratio.

6.53 The submission stated that the administration of Xeomin would be included under the same MBS services used for the current administration of Botox and Dysport for the same indications. Given that Xeomin would replace Botox at a 1:1 ratio, the net impact on the MBS would be neutral. However, since Xeomin would replace Dysport at a 2.5:1 ratio, the net MBS services would decrease slightly. This was reasonable.

6.54 Only injection fees (MBS items 18354 and 18361) were assumed to be relevant when estimating net changes to MBS due to the substitution of Dysport by Xeomin. This was reasonable. An application was made to MSAC to amend the existing MBS item codes 18354 and 18361 for botulinum toxin injections to include Xeomin by name to enable its identical use as Botox and Dysport (Application 1808 refers).

6.55 Table 12 presents the estimated financial implications for the PBS listing of Xeomin for spasticity based on the DPMQs for Botox (PBS items 10998W and 10999X, DPMQ = $1,098.67), Dysport 300 U (PBS items 10981Y and 12214W, DPMQ = $958.79) and Dysport 500 U (PBS items 11006G and 12178Y, DPMQ = $855.99).

Table 12: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated scripts of Xeomin						
Xeomin for dynamic equinus foot deformity	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][2]
Xeomin for moderate to severe spasticity of the upper limb	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Total	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]
Changes in scripts for Botox and Dysport						
Botox (10998W)	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]
Botox (10999X)	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]
Dysport (10981Y)	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]
Dysport (11006G)	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]
Dysport (12178Y)	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]
Dysport (12214W)	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]
Total	-[redacted][1]	-[redacted][a1]	-[redacted][a2]	-[redacted][2]	-[redacted][2]	-[redacted][2]
Estimated financial implications of Xeomin						
Net cost to the PBS/RPBS less copayments	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Estimated financial implications for Botox and Dysport						
Net cost to the PBS/RPBS less copayments	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]
Net financial implications						
Net cost to PBS/RPBS	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]
Net cost to MBS	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]
Net cost to the Australian Government	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]

Source: Tables 4.3.3, p85; 4.3.5, p86; 4.4.1-4.4.2, p87; 4.5.1, p88; 52, p89; 60 p89 of the submission.
MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

[a] The minor discrepancy in the total resulted from rounding adjustments.

The redacted values correspond to the following ranges:
[1] < 500
[2] 500 to < 5,000
[3] $0 to < $10 million

6.56 The net financial impact of listing Xeomin for spasticity to the Australian Government was estimated to be a net save of $0 to < $10 million in 2025 (Year 1), increasing to a net save of $0 to < $10 million by 2030 (Year 6). The estimated total savings were $0 to < $10 million over 6 years. The savings resulted from a slight reduction in the number of scripts processed for Xeomin compared to Dysport, given the equi-effectiveness of 1:2.5.

6.57 The submission identified the uptake rate as a potential source of uncertainty (see Table 13). During the evaluation, the following further sensitivity analyses were undertaken:

- Increase in uptake rates by [redacted]% from the base case.

- A constant increase of % in scripts per year (i.e. botulinum market growth rate based on the 2023-2024 period).

Table 13: Results of one-way sensitivity analyses

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Base case						
Net cost to Government	**-$[1]**	**-$[1]**	**-$[1]**	**-$[1]**	**-$[1]**	**-$[1]**
Higher uptake rate (+ % in each year)[a]						
Net cost to Government	-$[1]	-$[1]	-$[1]	-$[1]	-$[1]	-$[1]
% Change from base case [b]	20%	20%	20%	20%	20%	20%
Lower uptake rate (- % in each year)[a]						
Net cost to Government	-$[1]	-$[1]	-$[1]	-$[1]	-$[1]	-$[1]
% Change from base case [b]	-20%	-20%	-20%	-20%	-20%	-20%
Higher uptake rate (+ % from base case)[a,b]						
Net cost to Government	-$[1]	-$[1]	-$[1]	-$[1]	-$[1]	-$[1]
% Change from base case	50%	-25%	50%	50%	50%	50%
Botulinum toxin market growth rate of 10% for all years (Base case:4.10% in all years)[b]						
Net cost to Government	-$[1]	-$[1]	-$[1]	-$[1]	-$[1]	-$[1]
% Change from base case	0%	6%	12%	18%	25%	32%

Source: Table 4.7.1, pp89-90 of the submission, sheet 'Botulinum Toxin PBS Services' of the Workbook 4.
[a] Base case uptake rates: % in Year 1, % in Year 2, % in Years 3-4 and % in Years 5-6
[b] Added during the evaluation.
The redacted values correspond to the following ranges:
[1] $0 to < $10 million

6.58 The net financial implications for Government were sensitive to the botulinum toxin market growth rate. Assuming a constant % growth rate for the botulinum toxin market, the cost savings to Government increased by 21% over 6 years. It was also sensitive to the higher uptake rate (+% from the base case).

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

7 PBAC Outcome

7.1 The PBAC recommended the Authority required (STREAMLINED) listing of incobotulinumtoxinA (Xeomin®), on the basis that it should be available only under special arrangements under Section 100 (Botulinum Toxin Program), for the treatment of moderate to severe spasticity of the upper limb and dynamic equinus foot deformity in patients with cerebral palsy. The PBAC's recommendation for listing was based on, among other matters, its assessment that Xeomin would be cost-effective if it cost no more than the lowest cost alternative therapy – botulinum toxin type A (Botox®) or clostridium botulinum type A toxin-haemagglutinin complex (Dysport®).

7.2 The PBAC considered that the nominated comparator of Botox was appropriate. The PBAC considered that Dysport was also an alternative therapy.

7.3 The PBAC noted there were no direct head-to-head trials comparing Xeomin and Botox for upper and lower limb spasticity and that the submission was based on

unadjusted comparisons between results of two Xeomin trials (TIM and ZARA) and four Botox trials (Flett 1999, Fehlings 2000, Lowe 2006 and Russo 2007). The PBAC noted that TIM was a randomised, double-blind dose-response trial evaluating the efficacy and safety of 100 U, 200 U and 400 U Xeomin doses for the treatment of lower limb spasticity in patients aged 2-17 years with cerebral palsy. The PBAC noted that ZARA was a prospective randomised, double-blind dose-response trial evaluating the efficacy and safety of 50 U, 150 U and 200 U Xeomin doses for the treatment of upper limb spasticity alone or combined upper and lower limb spasticity in patients aged 2-17 years with cerebral palsy.

7.4 The PBAC acknowledged the limitations of the unadjusted comparisons noting there were key differences between the trials in dosing regimens, outcome measures and patient characteristics. However, overall, the PBAC considered that the claim of non-inferior effectiveness and safety to Botox was reasonable. The PBAC noted that in its previous consideration of Dysport for the treatment of moderate to severe focal spasticity of the upper limb in patients with cerebral palsy, it considered Dysport was likely non-inferior to Botox in terms of efficacy and safety while acknowledging there were limitations with the comparisons such as heterogeneity (paragraph 7.7, Dysport PSD, July 2020 PBAC meeting). In addition, the PBAC recalled that when it recommended listing Xeomin for post-stroke upper limb spasticity on the basis of a cost-minimisation approach with Botox, it considered that both agents would likely have similar clinical effects as they are analogues of each other (paragraph 6.17, Xeomin PSD, July 2014 PBAC meeting).

7.5 The PBAC noted that the Xeomin and Botox trials were conducted in the paediatric population. The PBAC agreed with the ESC in considering that, provided fixed contractures had not developed, there would be no clinical reason to expect a lack of effectiveness in adults and noting that, given the nature of the therapy, treatment was unlikely to be continued if no effect was observed.

7.6 The PBAC noted that the submission presented a cost-minimisation approach between Xeomin and Botox based on a proposed equi-effective dose of Xeomin 1 U = Botox 1 U, which was consistent with its previous recommendation for Xeomin and Botox across several indications (paragraph 7.3, Xeomin PSD, July 2014 PBAC meeting). The PBAC considered that Dysport was also an alternative therapy to Xeomin. The PBAC noted that the pre-PBAC Response proposed that Xeomin have a higher price than Dysport, calculated using the prices of Dysport and Botox weighted by market share. The PBAC noted it had previously considered Botox and Dysport to have non-inferior efficacy and safety for the treatment of moderate to severe focal spasticity of the upper limb in patients with cerebral palsy (paragraph 7.2, Dysport PSD, July 2020 PBAC Meeting). The evidence presented in the submission did not satisfy the PBAC that Xeomin would be more effective or safe than Dysport. The PBAC noted the submission's claim that the structure of incobotulinum toxin may reduce

immunogenic responses compared to alternative botulinum toxin products. However, the submission did not demonstrate how many, or to what extent, patients may benefit from this. Further, the PBAC recalled that it had previously considered Xeomin to be non-inferior to Botox and Dysport for other indications. The PBAC therefore did not consider a higher price than Dysport was justified. It advised that Xeomin should be listed on a cost-minimisation basis against the least costly alternative therapy (Dysport or Botox).

7.7 The PBAC noted the Pre-Sub-Committee Response claimed that dose relativity for Botox and Dysport varies from 1:2 to 1:9. The PBAC reaffirmed its previous advice that equi-effective doses based on maximum quantities dispensed should be used (paragraph 7.10, Dysport PSD, July 2020 PBAC meeting). The PBAC advised that the equi-effective doses were:

Xeomin 1 U = Botox 1 U

Xeomin 1 U = Dysport 2.5 U

7.8 The PBAC advised that the Xeomin restrictions should be consistent with the current Botox and Dysport restrictions for moderate to severe spasticity of the upper limb and dynamic equinus foot deformity in patients 2 years and older with cerebral palsy.

7.9 PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because Xeomin is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over Botox and Dysport, and not expected to address a high and urgent unmet clinical need given the presence of alternative therapies, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.

7.10 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new listings as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
INCOBOTULINUMTOXINA					
incobotulinumtoxinA 100 units injection, 1 vial	NEW	4	4	0	Xeomin
Category / Program: ☒ Section 100 – Botulinum Toxin Program (Code MF)					
Prescriber type: ☒ Medical Practitioners					
Benefit type: ☒ Authority Required (STREAMLINED) [5359/ 8822]					
Prescribing rule level:					
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.					
Restriction Summary 8901 / Treatment of Concept: 5359					
Indication: Dynamic equinus foot deformity					
Clinical criteria:					
The condition must be due to spasticity,					
AND					
Clinical criteria:					
Patient must have cerebral palsy,					
AND					
Clinical criteria:					
Patient must be ambulant.					
Treatment criteria:					
Must be treated by a neurologist; OR					
Must be treated by an orthopaedic surgeon; OR					
Must be treated by a paediatrician; OR					
Must be treated by a rehabilitation specialist.					
Population criteria:					
Patient must be aged from 2 to 17 years inclusive.					
Restriction Summary 8930 / Treatment of Concept: 8822					
Indication: Dynamic equinus foot deformity					
Clinical criteria:					
The condition must be due to spasticity,					
AND					
Clinical criteria:					
Patient must have cerebral palsy,					
AND					
Clinical criteria:					

Patient must be ambulant.
Treatment criteria:
Must be treated by a neurologist; OR
Must be treated by an orthopaedic surgeon; OR
Must be treated by a paediatrician; OR
Must be treated by a rehabilitation specialist.
Population criteria:
Patient must be at least 18 years of age.

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
INCOBOTULINUMTOXINA					
incobotulinumtoxinA 100 units injection, 1 vial	NEW	4	4	0	Xeomin
Category / Program: ☒ Section 100 – Botulinum Toxin Program (Code MF)					
Prescriber type: ☒ Medical Practitioners					
Benefit type: ☒ Authority Required (STREAMLINED) [5178/ 8929]					
Prescribing rule level:					
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.					
Restriction Summary 8821 / Treatment of Concept: 5178					
Indication: Moderate to severe spasticity of the upper limb					
Clinical criteria:					
Patient must have cerebral palsy.					
Treatment criteria:					
Must be treated by a neurologist; OR					
Must be treated by an orthopaedic surgeon; OR					
Must be treated by a paediatrician; OR					
Must be treated by a rehabilitation specialist, OR					
Must be treated by a plastic surgeon.					
Population criteria:					
Patient must be aged from 2 to 17 years inclusive.					
Restriction Summary 8928 / Treatment of Concept: 8929					
Indication: Moderate to severe spasticity of the upper limb					
Clinical criteria:					
Patient must have cerebral palsy.					
Treatment criteria:					
Must be treated by a neurologist; OR					
Must be treated by an orthopaedic surgeon; OR					
Must be treated by a paediatrician; OR					
Must be treated by a rehabilitation specialist, OR					

Must be treated by a plastic surgeon.
Population criteria:
Patient must be at least 18 years of age.

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 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.

10 Sponsor's Comment

The sponsor had no comment.