6.07 INCOBOTULINUM TOXIN A, Lyophilised powder for solution for injection, 100 units, Xeomin®, Merz Australia Pty Ltd.

1 Purpose of submission

1.1 The Category 2 streamlined codependent submission requested a Section 100, PBS Botulinum Toxin Program, Authority Required Streamlined listing for incobotulinumtoxinA (Xeomin) for the treatment of moderate to severe spasticity of the lower limb in adults following stroke, traumatic brain injury, or spinal cord injury.

1.2 A submission to the MSAC is required to amend existing MBS item code 18360 to include incobotulinumtoxinA.

1.3 Listing was requested on the basis of a cost-minimisation approach versus botulinum toxin type A (Botox).

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

Component	Description
Population	Adults with moderate to severe unilateral lower limb spasticity (MAS ≥2) following stroke, traumatic brain injury, or spinal cord injury, with functional impairment affecting mobility, activities of daily living, or quality of life.
Intervention	IncobotulinumtoxinA, purified Botulinum toxin type A
Comparator	Botulinum toxin type A (BOTOX®)
Outcomes	Efficacy endpoints: • Change from baseline in Modified Ashworth Scale (MAS) plantar flexors score to end of Week 12 • Change from baseline in MAS-PF to Weeks 4, 6, and 8 • Responders defined as an improvement of at least 1 point in MAS plantar flexors Primary safety endpoints: • Incidence of treatment emergent AEs (TEAEs), TEAEs of special interest, (TEAESIs) and serious TEAEs.
Clinical claim	IncobotulinumtoxinA is noninferior to Botulinum toxin type A for treatment of moderate to severe spasticity of the lower limb following an acute event

Source: Table 1.1.1, p4 of the submission.

2 Background

Registration status

2.1 IncobotulinumtoxinA (Xeomin) was TGA registered on 8 May 2025 for the additional indication of treatment in adults of unilateral spasticity of the lower limb affecting the ankle joint.

2.2 IncobotulinumtoxinA (Xeomin) is registered in the USA, Canada, New Zealand, Singapore and Switzerland and the EU. In the US and Europe the approved indications

do not include spasticity of the lower limb and in Canada they include only lower limb spasticity due to stroke.

Previous PBAC consideration

2.3 PBAC has not previously considered Xeomin for lower limb spasticity due to stroke or other acute events.

2.4 Xeomin was most recently considered in July 2025 for the treatment of upper limb spasticity and equinus foot deformity in patients with cerebral palsy.

2.5 There have been a number of previous PBAC considerations of botulinum toxin preparations for spasticity in upper and lower limbs following stroke or other acute neurological events.

2.6 Botox was recommended for listing for the treatment of upper limb spasticity following stroke in July 2008.

2.7 In July 2014 PBAC recommended listing of Xeomin for blepharospasm, cervical dystonia and post-stroke spasticity of the upper limb (Paragraph 7.1, Xeomin Public Summary Document [PSD], July 2014 PBAC Meeting).

2.8 In March 2019 PBAC recommended the listing of Botox for treatment of lower limb spasticity following stroke or other acute neurological event. Dysport was recommended for listing for lower limb spasticity following stroke or other acute neurological event in July 2019.

2.9 In November 2019 PBAC recommended the extension of listing for upper limb spasticity following stroke to upper limb spasticity following other acute events, considering that "despite the lack of clinical trials in aetiologies other than stroke, the request to extend the listing of botulinum toxins to include acute events was reasonable and biologically plausible" (Paragraphs 5.11, 6.1, Xeomin PSD, November 2019 PBAC Meeting; see also Paragraph 5.2, Botox PSD, March 2019 PBAC Meeting).

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

3 Requested listing

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 ~~powder for solution for injection~~	NEW	4	4	0	Xeomin
	Category / Program: ☒ Section 100 – Botulinum Toxin Program (Code MF)				
	Prescriber type: ☒ Medical Practitioners				
	Restriction type: ☒ Authority Required (Streamlined) [new/existing code]				
	Administrative Advice:				

		The units used to express the potency of botulinum toxin preparations currently available for PBS subsidy are not equivalent.
		Caution: *Contraindications to treatment include known sensitivity to botulinum toxin.*
		Administrative Advice: *Special Pricing Arrangements apply.*
		Indication: Moderate to severe spasticity of the lower limb following an acute event
		Clinical criteria:
		The condition must be moderate to severe spasticity of the lower limb/s following stroke or other acute neurological event, defined as a Modified Ashworth Scale rating of 3 or more,
		AND
		Clinical criteria:
		The treatment must only be used as second line therapy when standard management has failed; OR
		The treatment must only be used as an adjunct to physical therapy
		AND
		Clinical criteria:
		The treatment must not continue if the patient does not respond (defined as not having had a decrease in spasticity rating of at least 1, using the Modified Ashworth Scale, in at least one joint) after two treatment periods (with any botulinum toxin type A)
		AND
		Clinical criteria:
		Patient must not have established severe contracture in the limb to be treated,
		AND
		Clinical criteria:
		The treatment must not exceed a maximum of 4 treatment periods (with any botulinum toxin type A) per lower limb in the first year of treatment, and 2 treatment periods with any botulinum toxin type A) per lower limb each year thereafter.
		Treatment criteria:
		Must be treated by a neurologist; OR
		Must be treated by an orthopaedic surgeon; OR
		Must be treated by a rehabilitation specialist; OR
		Must be treated by a plastic surgeon; OR
		Must be treated by a geriatrician
		Population criteria:
		Patient must be ~~aged 18 years or older~~ *at least 18 years of age.*
		Administrative Advice: Standard management includes physiotherapy and/or oral spasticity agents.
		Administrative Advice: *An acute event may be clinical external event that leads to upper motor neuron lesions resulting in spasticity for example stroke, traumatic brain injury, spinal cord injury, infection or hypoxia.*

Category / Program: Section 100
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐
Restriction type: ☒Authority Required (STREAMLINED)
Condition: Moderate to severe spasticity of the lower limb following an acute event
Treatment Phase: Initial and continuing
Clinical criteria:
The condition must be moderate to severe spasticity of the lower limb/s following stroke or other acute neurological event, defined as a Modified Ashworth Scale rating of 3 or more,
AND
Clinical criteria:
The treatment must only be used as second line therapy when standard management has failed;
OR
The treatment must only be used as an adjunct to physical therapy,
AND
The treatment must not continue if the patient does not respond (defined as not having had a decrease in spasticity rating of at least 1, using the Modified Ashworth Scale, in at least one joint) after two treatment periods (with any botulinum toxin type A),
AND
Patient must not have established severe contracture in the limb to be treated,
AND
The treatment must not exceed a maximum of 4 treatment periods (with any botulinum toxin type A) per lower limb in the first year of treatment, and 2 treatment periods (with any botulinum toxin type A) per lower limb each year thereafter.
Treatment criteria:
Must be treated by a neurologist; OR
Must be treated by an orthopaedic surgeon; OR
Must be treated by a rehabilitation specialist; OR
Must be treated by a plastic surgeon; OR
Must be treated by a geriatrician
Population criteria:
Patient must be aged 18 years or older.
Administrative Advice: Standard management includes physiotherapy and/or oral spasticity agents.

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

3.2 The submission requested a Special Pricing Arrangement for Xeomin for this indication, consistent with existing listings.

3.3 The TGA approval is for the treatment of spasticity, regardless of the underlying cause.

3.4 The restriction, based on current restrictions for Botox® and Dysport®, confines use to patients with stroke, spinal cord injury, or traumatic brain injury. This is not strictly consistent with the population in the submitted trials, because the trials included only patients with stroke. It is also not a consequence of the pathophysiology of spasticity or the mechanism of action of botulinum toxin. If the listing of botulinum toxins can be extended to include acute events, this raises the question of whether the same could be done for chronic conditions (i.e. patients with spasticity due to conditions such as multiple sclerosis, and for adults with cerebral palsy). The pre-PBAC response stated that the submission is for the same indication as the existing Botox® and

Dysport® listings with proposed restriction wording that has already been accepted by the PBAC.

3.5 The submission inconsistently described the severity of spasticity required for the proposed listing, with a Modified Ashworth Scale score of at least 2 in Table 1.1.1 of the submission but of at least 3 in Table 1.4.2.

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

4 Population and disease

4.1 Spasticity is increased muscle tone, detected on physical examination as resistance to passive muscle stretch that increases with greater velocity of muscle stretching. It commonly affects mainly the flexor muscles of the upper limb and the extensor muscles of the trunk and lower limb.

4.2 Spasticity is due to interruption of descending inhibition of spinal motor neurones. As a result, many neurological diseases cause spasticity in adults. The commonest are stroke, traumatic brain injury, spinal cord injury, multiple sclerosis and cerebral palsy (the last two are excluded from the current submission).

4.3 A common and functionally important result of lower limb spasticity is fixed plantar flexion of the ankle - "pes equinus" - limiting mobility and increasing the need for assistive devices and personal assistance.

4.4 Botulinum toxin blocks the release of acetylcholine at the neuromuscular junction, which weakens the muscle. It does not affect the underlying neural processes that cause spasticity.

4.5 The submitted treatment algorithm is that for children and adolescents with pes equinus, which is uncommonly due to stroke or traumatic brain or spinal cord injury. This algorithm proposes that all patients with focal spasticity and MAS score ≥2 (not ≥3 as proposed for listing) would receive botulinum toxin as first-line treatment. This is not consistent with the proposed restriction, which requires failure of standard management.

4.6 It was stated by the submission that the proposed algorithm "reflects [...] current Australian clinical guidelines", but no reference was provided. Australian Stroke Foundation guidelines suggest that "Interventions to reduce spasticity should be considered when the level of spasticity interferes with activity or the ability to provide care to the stroke survivor" and that "with lower limb spasticity, Botulinum Toxin A in addition to rehabilitation therapy may be used to reduce spasticity but is unlikely to improve motor function or walking".[1]

4.7 There are seven antigenically distinct botulinum toxins, Types A to G, of which Types A and B are used in medicine. Xeomin is a preparation of botulinum toxin Type A, with

[1] https://informme.org.au/guidelines/living-clinical-guidelines-for-stroke-management accessed 29 November 2025.

the non-proprietary name incobotulinumtoxinA.[2] Xeomin contains only the 150 kD toxin, without the neurotoxin-associated proteins (also called hemagglutinins and complexing proteins) present in the native botulinum toxin complex and retained in Botox (onabotulinumtoxinA) and Dysport (abobotulinumtoxinA). The submission suggested that because Xeomin does not contain the neurotoxin-associated proteins it has a lower risk of immunogenic responses and secondary failure but this is not well supported by evidence.[3]

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

5 Comparator

5.1 Botox (onabotulinumtoxinA) was nominated as the primary comparator and Dysport (abobotulinumtoxinA) as the secondary comparator. These comparators were reasonable because the PBAC has previously advised that Botox, Dysport and Xeomin should be treated as interchangeable on an individual patient basis (Paragraph 6.15, Xeomin PSD, November 2019 PBAC Meeting).

5.2 OnabotulinumtoxinA and abobotulinumtoxinA are listed on the PBS for the proposed population. If listed, incobotulinumtoxinA would be used in place of these therapies if chosen by the prescriber.

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 inputs

6.2 The PBAC noted that no consumer inputs were received for this item.

Clinical trials

6.3 The submission stated that it was based on one pivotal trial of Xeomin (Study 3098) and 2 trials of Botox (REFLEX and Trial 512).

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[2] Nomenclature of botulinum toxin preparations is confused. IncobotulinumtoxinA, onabotulinumtoxinA and abobotulinumtoxinA are US Adopted Names, unique to Xeomin, Botox and Dysport respectively. Outside the US the usual non-proprietary name, applied to all preparations, is Botulinum Toxin Type A. Botox and Dysport are listed on the ARTG *only* under Botulinum Toxin Type A and searches for onabotulinumtoxinA and abobotulinumtoxinA produce no results. Xeomin, however, is listed *only* under incobotulinumtoxinA and a search for Botulinum Toxin Type A does not produce the ARTG entry for Xeomin. Previous PBAC Public Summary Documents have used the trade names, and this practice will be generally used in the Commentary.

[3] Carruthers JD. Overview of botulinum toxin for cosmetic indications, Immunogenicity. In: UpToDate, Connor RF (ed) Wolters Kluwer, Accessed 12 January 2026.

6.4 Two randomised controlled trials of Xeomin for the treatment of lower limb spasticity have been completed, Study 3098 and Study 3002. Study 3002 was included only as supporting evidence of safety. No justification for not including the efficacy data from 3002 was included. The TOWER study was an uncontrolled dose-titration study of Xeomin in patients with upper or lower limb spasticity, and a post-hoc analysis of patients with lower limb spasticity was included as evidence of safety, although no safety data were reported in the included publication.

6.5 Comparison with Botox was an indirect treatment comparison with placebo as common comparator, using only 3098.

6.6 Although Dysport (abobotulinumtoxinA) was nominated as a comparator, no comparison with Dysport was presented, though there is a randomised, placebo-controlled trial of Dysport in lower-limb spasticity reporting comparable outcomes.[4]

6.7 Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol/Publication Title	Reference
Xeomin Trials		
3098 J-PLUS	Prospective, double-blind, placebo-controlled, randomized, multi-center study with an open-label lead-in tolerability period and an open-label extension period to investigate the efficacy and safety of NT 201 in the treatment of post-stroke spasticity of the lower limb. Masakado Y, Kagaya H, Kondo K, et al. Efficacy and Safety of IncobotulinumtoxinA in the Treatment of Lower Limb Spasticity in Japanese Subjects.	2020 *Front Neurol* 2022; 13:832937.
3002 NCT01464307	Prospective, double-blind, placebo-controlled, randomized, multi-center study with an open-label extension period to investigate the efficacy and safety of NT 201 in the treatment of post-stroke spasticity of the lower limb.	2016
TOWER NCT01603459	Bensmail D, Wissel J, Laffont I, et al. Efficacy of incobotulinumtoxinA for the treatment of adult lower-limb post-stroke spasticity, including pes equinovarus	Ann Phys Med Rehab 2021; 64:101376.
Botox Trials		
REFLEX NCT01575054	Wein T, Esquenazi A, Jost WH, Ward AB, Pan G, Dimitrova R. OnabotulinumtoxinA for the treatment of poststroke distal lower limb spasticity: A randomized trial.	*PM&R* 2018; 10:693-703.
512 NCT00460655	Kaji R, Osaka Y, Suyama K, et al. Botulinum toxin type A in post-stroke lower limb spasticity: a multicenter, double-blind, placebo-controlled trial.	*J Neurol* 2010; 257:1330-1337.

Source: Table 2.2.2, p22 of the submission.

6.8 The key features of the randomised trials are summarised in Table 3.

[4] Gracies JM, Esquenazi A, Brashear A, et al. Efficacy and safety of abobotulinumtoxinA in spastic lower limb: Randomized trial and extension. *Neurology* 2017; 898:2245-2253.

Table 3: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Xeomin vs Placebo						
3098	208	R, DB, MC (all Japan); fixed dose Xeomin 400U across affected muscles; 12 wk with OLE up to 40 wk.	Low	Ages 20-80, unilateral pes equinus after stroke ≥6 m previously causing gait impairment; MAS ≥3 in plantar flexors.	CFB in MAS for plantar flexors to 12 wk calculated as AUC for wks 1,4,6,8,12.	Used
3002	287	R, DB, MC; fixed dose Xeomin 400U across affected muscles; 12 wk with OLE up to 36 wk.	Low	Ages 18-80; pes equinovarus due to stroke at least 3 m previously causing gait impairment; AS ≥2 in plantar flexors.	CFB in AS to 4 wk; Investigator's GAE at 12 wk.	Not used
Botox vs Placebo						
REFLEX	468	R, DB, MC; 12 wk with OLE.	Low	Ages 18-65; MAS ≥3 ≥3 m after stroke.	CFB MAS mean score 4 and 6 wk; Investigator's CGI Change.	Used
512	120	R (method not adequately described), DB, MC (all Japan); 300U across affected muscles.	Unclear	Ages 20-80; pes equinus due to stroke ≥6 m previously; MAS ≥3 in ankle flexors.	CFB MAS AUC at 1,2, 4, 6, 8, 12 wk; MAS CFB.	Used

Source: Constructed during the evaluation from CSRs and published reports.
AS = Ashworth score; AUC = area under curve; CFB = change from baseline; CGI = clinical global impression; DB = double blind; m = month; MAS = modified Ashworth score; MC = multi-centre; OL = open label; R = randomised; wk = week.

6.9 An important design feature of the Xeomin trials was that previous botulinum toxin treatment for spasticity was allowed, provided only that the most recent injection was more than 16 weeks before enrolment. In 3002 74/289 patients (26%) and in 3098 109/208 patients (52%) had previously received botulinum toxin, of whom 56/74 (76%) and 103/109 (94%) respectively had been treated for lower limb spasticity.

6.10 Most patients in 3002 had received multiple botulinum toxin treatments (median 3.0, range 0, 19); this information was not provided for 3098. The median (range) time since most recent treatment was 7.5 (4, 166) months in 3002 and 5.0 (4, 65) months in 3098, so it appears that treatment for most pre-treated patients was ongoing at the time of enrolment in the Xeomin trials. This may have resulted in patients with a prior good response to botulinum toxin being selectively included, especially in 3098, which could have increased the likelihood of a response to Xeomin.

6.11 Previous treatment with botulinum toxin was allowed in REFLEX provided the last injection was more than 20 weeks before enrolment but was an exclusion criterion in 512.

6.12 In terms of other baseline characteristics of the patients in the trials, the most obvious difference is that all patients in 3098 and Kaji, 2010 were Japanese, while a large majority of patients in the other trials were white. Patients in 3002 had suffered their most recent stroke more recently (mean about 4.5 years) than patients in the other trials (mean 6 to 7 years).

Comparative effectiveness

6.13 Efficacy outcomes in the trials are shown in **Error! Reference source not found.** and Table 5.

6.14 Study 3098 reported the Modified Ashworth Score and 3002 the original version. The scales differ only in that the modified scale divided the original scale's point 1 (= Slight increase in tone giving a catch when the limb is moved) into 1 and 1+ (1 = Slight increase in muscle tone, with a catch and release or minimal resistance at the end of the range of motion; 1+ = Slight increase in muscle tone, manifested by a catch, followed by minimal resistance through the remainder - less than half - of the range of motion). Points 2, 3 and 4 remained the same.

6.15 The inclusion criteria for 3002 included an Ashworth Scale score of at least 2 in the plantar flexors, and the inclusion criteria for 3098 included a Modified Ashworth Scale score of at least 3 in the plantar flexors. In order to provide data usable in statistical analyses the Modified Ashworth Scale is made a 6-point scale, with scores 1 and 1+ recorded as 1 and 2, so MAS = 3 is the same as AS = 2 - ie, the inclusion criteria for the studies were the same.

6.16 The PBAC has previously accepted that trials using changes in Ashworth Scale and trials using changes in Modified Ashworth Scale scores can be compared in indirect treatment comparisons (Table 5, Paragraph 6.11, Table 7, Paragraph 6.17, Dysport PSD, July 2020 PBAC Meeting), although in its most recent consideration the committee expressed reservations about this approach (Paragraph 6.17, Xeomin PSD, July 2025 PBAC Meeting).

6.17 The Clinical Global Impression is a 9-point or 11-point Likert scale with -4 or -5 indicating the worst possible condition and +4 or +5 the best possible condition, so positive change from baseline indicates improvement.

6.18 The Physician Rating Scale for gait rates initial foot contact (toe = 0 to heel = 3), foot contact at mid-stance (toe to toe = -1 to heel to toe = 3) and need for assistive devices (walker and assistance = 0 to none = 3), giving a total score of -1 to 9 with positive change from baseline indicating improvement.

6.19 The change in Modified Ashworth Score (MAS) in 3098 over time is shown in Figure 1 (although the points are equally spaced they correspond to weeks 1, 4, 6, 8 and 12). The differences versus placebo were statistically significant at 4, 6, and 8 weeks but not at 1 and 12 weeks. This figure differs from Figure 2.5.1 of the submission, which was taken from the published report of this trial and shows least squares mean change and standard errors and omits data for week 1.

6.20 The largest difference in CGI, PRS and walking speed between Xeomin and placebo was observed at four weeks. The PBAC has previously advised that outcomes at 4 and 12 weeks would be relevant for assessment of botulinum toxin treatment of spasticity.

Table 4: Efficacy outcomes in the submitted Xeomin trials

	3098		3002	
	Xeomin N = 104	Placebo N = 104	Xeomin N = 144	Placebo N = 145

AUC of CFB MAS at ankle, weeks.points, Mean (SD) LS Mean (SE) LS Mean Difference vs Placebo (95% CI)	 -7.7 (7.0) -8.4 (0.7) -2.6 (-4.4, -0.8)	 -4.8 (5.8) -5.8 (0.7) -	NR	NR
MAS/AS Baseline, Mean (SD)	3.0 (NA)[1]	3.0 (NA)[1]	2.8 (0.7)	2.8 (0.7)
MAS/AS at 4 weeks, Mean (SD)	NR	NR	2.4 (0.9)	2.4 (0.8)
MAS/AS CFB to 4 weeks, LS mean difference vs placebo (95% CI)	-0.24 (-0.43, -0.05)	-	0.0 (-0.1, 0.2)	-
MAS/AS at 12 weeks, Mean (SD)	NR	NR	2.7 (0.8)	2.7 (0.7)
MAS/AS CFB to 12 weeks, LS mean difference vs placebo (95% CI)	-0.1 (-0.3, 0.04)	-	-0.1 (-0.2, 0.1)	-
CFB MAS ³1, n (%) Week 1 Week 4 Week 6 Week 8 Week 12	 44 (42.3%) 58 (55.8%) 62 (59.6%) 55 (52.9%) 37 (35.6%)	 31 (29.8%) 43 (41.3%) 41 (39.4%) 35 (33.7%) 26 (25.0%)	 NR 53 (36.8%) NR 55 (38.2%) 27 (18.8%)	 NR 51 (35.2%) NR 48 (33.1%) 24 (16.6%)
CFB MAS ³2, n (%) Week 1 Week 4 Week 6 Week 8 Week 12	 6 (5.8%) 11 (10.6%) 14 (13.5%) 13 (12.5%) 3 (2.9%)	 3 (2.9%) 3 (2.9%) 6 (5.8%) 3 (2.9%) 2 (1.9%)	 NR 9 (6.3%) NR 10 (7.1%) 4 (3.0%)	 NR 10 (6.9%) NR 7 (4.9%) 6 (4.3%)
Investigator's GAE at 12 weeks, n (%) Very Good Good Moderate Poor	NA	NA	 5 (3.5%) 41 (28.5%) 32 (22%) 66 (46%)	 7 (5%) 33 (23%) 36 (27%) 66 (46%)
Investigator's CGI CFB to 4 weeks Mean (SD) LS mean (SE) LS mean difference vs placebo (95% CI)	 1.4 (1.9) 1.4 (0.2) 0.0 (-0.5, 0.4)	 1.2 (2.0) 1.4 (0.2) -	NA	NA
Investigator's CGI CFB to 12 weeks Mean (SD) LS mean (SE) LS mean difference vs placebo (95% CI)	 0.8 (1.5) 0.8 (0.2) -0.1 (-0.5, 0.3)	 0.7 (1.7) 1.0 (0.2) -	NA	NA
Patient's CGI CFB to 4 weeks Mean (SD) LS mean (SE) LS mean difference vs placebo (95% CI)	 0.9 (0.21) 0.8 (0.2) 0.1 (-0.7, 0.3)	 0.7 (2.3) 0.8 (0.2) -	NA	NA

Patient's CGI CFB to 12 weeks Mean (SD) LS mean (SE) LS mean difference vs placebo (95% CI	 0.5 (1.8) 0.5 (0.2) -0.2 (-0.7, 0.3)	 0.5 (2.1) 0.6 (0.2) -	NA	NA
CFB to week 4 PRS Gait score Mean (SD) LS mean (SE) LS mean difference vs placebo (95% CI)	 0.6 (1.3) 0.6 (0.2) 0.2 (-0.3, 0.6)	 0.3 (1.4) 0.5 (0.2) -	NA	NA
CFB to week 12 PRS Gait score Mean (SD) LS mean (SE) LS mean difference vs placebo (95% CI)	 0.1 (1.5) 0.1 (0.2) -0.5 (-1.0, -0.1)[2]	 0.4 (1.3) 0.6 (0.2) -	NA	NA
Time to walk 10m at preferred speed, baseline, seconds Mean (SD)	 17.0 (12.0)	 16.5 (14.4)	NA	NA
Time to walk 10m at preferred speed, CFB to 12 weeks, seconds Mean (SD) LS mean (SE) LS mean difference vs placebo (95% CI)	 -0.46 (6.4) -0.99 (1.0) -0.46 (-3.0, 2.1)	 -0.03 (7.4) -0.53 (1.0) -	NA	NA

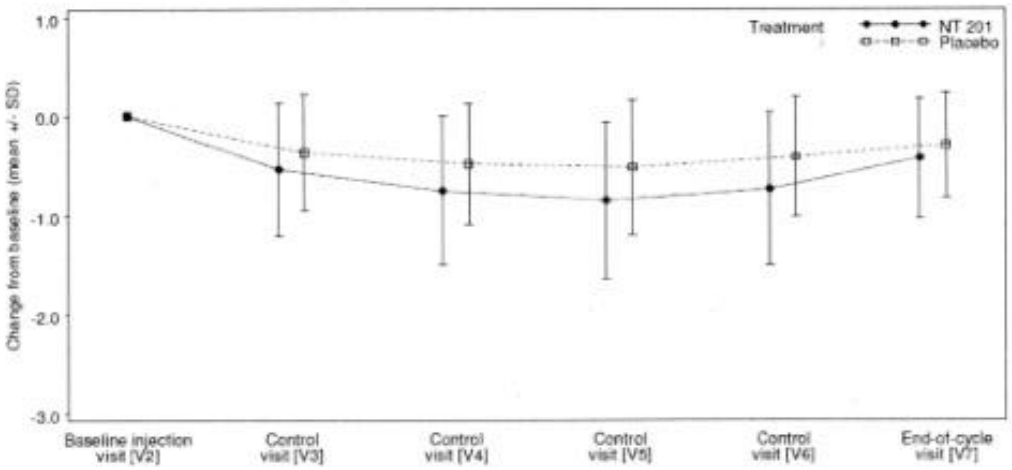
Source: Tables 31, 33, 35, 36, 41, 3098 CSR; Tables 15, 24, 27, 3002 CSR. Statistically significant results are in **bold**.

[1] Baseline MAS was 3 for all subjects.

[2] Note that this difference favours placebo.

AS = Ashworth Score; AUC = area under the curve; CFB = change from baseline; CGI = clinical global impression (range -5 = worst possible to 5 = best possible); CI = confidence interval; GAE = global assessment of efficacy; LS = least squares; MAS = modified Ashworth score; NA = not applicable; NR = not reported; PRS = physician's rating scale for gait (range -1 to 9, higher scores better); SD = standard deviation; SE = standard error.

Figure 1: Change in MAS over time in Study 3098



Source: 3098 CSR, Figure 4, p144/281.

6.21 The PBAC has previously accepted that a one-point improvement in MAS associated with functional improvement would be a reasonable minimum clinically important difference.

6.22 There was a consistent but modest difference between Xeomin and placebo in the proportions of patients in 3098 achieving a 1-point or 2-point change in MAS. This difference was statistically significant at weeks 4, 6 and 8, but not at weeks 1 and 12.

6.23 In 3002 there was no difference between Xeomin and placebo in the proportion of 1-point or 2-point falls in AS. In 3002 the placebo response was similar or slightly less than in 3098, but the rate of success in the Xeomin-treated group was less than in 3098.

6.24 In neither 3002 nor 3098 was there any effect of Xeomin on any functional outcome, so the effect of Xeomin versus placebo was less than the minimum clinically important difference in both trials.

6.25 In the trial considered by PBAC in July 2025 in relation to the use of Xeomin for equinus deformity due to cerebral palsy, the least squares mean change from baseline in Ashworth Scale scores at 8 weeks was about -0.7, similar to that reported in the trials included in the present submission (Table 7, Paragraph 6.20, Xeomin PSD, July 2025 PBAC Meeting). However, there was no placebo-treated group in that trial.

6.26 In 3098 two subjects negative for neutralising antibodies at baseline were positive at the end-of-study visit . In 3002 8/114 (7.0%) patients who had no previous treatment with botulinum toxin developed neutralising antibodies to botulinum toxin during treatment with Xeomin. There was no evidence of reduced effect of Xeomin in these patients . The incidence of neutralising antibodies in 3002 was higher than the pooled frequency of 1.8% reported from studies of all botulinum toxin preparations in a recent systematic review,[5] and apparently at variance with the statement in the submission, based on a systematic review funded by the sponsor (Walter, 2025) that there were no reports of neutralising antibodies in treatment-naive patients treated with Xeomin for spasticity .

6.27 The frequency of treatment failure caused by neutralising antibodies is difficult to estimate because there is no agreed definition of treatment failure, but it appears to be rare.

[5] Rahman E, Alhitmi HK, Mosahebi A. Immunogenicity to Botulinum Toxin Type A: A systematic review with meta-analysis across therapeutic indications. *Aesthetic Surg J 2022;* 42:106–120.

Table 5: Efficacy outcomes in the Botox trials

	REFLEX		512	
	Botox N = 233	Placebo N = 235	Botox N = 58	Placebo N = 62
AUC of CFB MAS, weeks.points, Mean (SD) Median (range) Mean Difference vs Placebo (95% CI)	NA	NA	-8.5 (6.7) -9.5 (-22, 0) -3.4 (-5.8, -1.0)	-5.1 (6.6) -2 (-25.5, 0) -
MAS at baseline, Mean (SD)	3.1 (NR)	3.1 (NR)	3.3 (0.45)	3.2 (0.4)
MAS CFB to 4 weeks, Mean (SD)	-0.8 (0.9)	-0.6 (0.8)	-0.9 (0.7)	-0.4 (0.7)
MAS CFB to 12 weeks, Mean (SD)	NR	NR	-0.6 (0.7)	-0.4 (0.6)
Patients with MAS CFB ³1 at 4 weeks, n (%)	121 (52.0%)	91 (38.9%)	NR	NR
Patients with MAS CFB ³1 at 8 weeks, n (%)	114 (48.9%)	93 (39.5%)	NR	NR
Patients with MAS CFB ³1 at 12 weeks, n (%)	75 (32.3%)	102 (23.0%)	NR	NR
Patients with MAS CFB ³2 at 4 weeks, n (%)	48 (20.7%)	34 (14.5%)	NR	NR
Investigator CGI at baseline Mean (SD)	NR	NR	-1.3 (1.7)	-1.3 (1.8)
Investigator CGI CFB to 4 weeks, Mean (SD)	0.9 (0.95)	0.65 (0.9)	1.1 (1.2)	0.6 (1.1)
Investigator CGI CFB to 12 weeks, Mean (SD)	NR	NR	0.8 (1.3)	0.5 (1.3)
Patient CGI at baseline Mean (SD)	NR	NR	-1.3 (1.9)	0.9 (2.0)
Patient CGI CFB to 4 weeks, Mean (SD)	NR	NR	0.8 (1.6)	0.4 (1.8)
Patient CGI CFB to 12 weeks, Mean (SD)	NR	NR	0.5 (1.5)	0.5 (2.2)
PRS Gait Score at baseline Mean (SD)	NR	NR	3.1 (2.4)	3.2 (2.0)
PRS Gait Score CFB to 4 weeks, Mean (SD)	NR	NR	0.5 (1.2)	0.6 (1.4)
PRS Gait Score CFB to 12 weeks, Mean (SD)	NR	NR	0.6 (1.3)	0.6 (1.6)
Time to walk 10 m at baseline, seconds Mean (SD)	NR	NR	61.0 (49.7)	52.8 (51.6)
Time to walk 10 m, CFB to 4 weeks, Mean (SD)	NR	NR	-6.1 (22.9)	-7.4 (20.8)
Time to walk 10 m, CFB to 12 weeks, Mean (SD)	NR	NR	-10.1 (26.9)	-8.5 (24.7)
Goal Attainment Scale, % 0 or better at 8 weeks	32.3%	30.3%	NR	NR

Source: Constructed during the evaluation from published reports. Statistically significant results vs placebo are in **bold**.

AUC = area under the curve; CFB = change from baseline; CGI = clinical global impression; CI = confidence interval; MAS = modified Ashworth scale; NR = not reported; PRS = physician's rating scale; SD = standard deviation.

6.28 The Goal Attainment Scale assesses achievement of a patient-defined goal, with 0 = achieved as desired, -1 a little less than desired, -2 a lot less than desired, +1 a little more than desired and +2 a lot more than desired. There was no difference between Xeomin and placebo in the proportion of patients with a Goal Attainment Score of at least 0.

6.29 Although numerical values were not reported, REFLEX reported no difference between placebo-treated and Botox treated patients in MAS scores or CGI scores at 12 weeks, or for walking speed at any time.

6.30 A trial of broadly similar design using Dysport (abobotulinumtoxinA) produced similar results.[6] Patients were randomised to placebo (N = 128) or Dysport 1000 U (N = 125) or 1500 U (N = 128). As in the Botox and Xeomin trials, there were slightly larger falls in MAS with active treatment than with placebo; these were statistically significant compared to placebo at 4 and 12 weeks for the 1500 U dose but not for the 1000 U dose. There were no statistically or clinically significant differences between either dose of Dysport and placebo in Clinical Global Impression, walking speed, or quality of life.

6.31 The open-label extensions of the trials showed consistent improvements in spasticity and in functional outcomes much larger than those seen in the double-blind phases. It has been suggested that there may be long-term processes of learning and adaptation that account for slow improvement in functional outcomes, but this is an ad hoc suggestion unsupported by evidence and bias is a more likely explanation.

Comparative harms

6.32 Adverse events in the Xeomin trials are shown in Table 6. Adverse events of special interest were symptoms suggestive of muscle weakness outside the target area caused by systemic spread of toxin absorbed from the site of injection, which can cause life-threatening or fatal iatrogenic botulism. Adverse events of special interest in the double-blind (one injection) and open-label extension phases (three injections) of 3098 and 3002 are shown. Also shown are adverse events and adverse events of special interest in TOWER, an uncontrolled dose-finding study of patients with either upper limb or lower limb spasticity who received a total of three injections.[7]

[6] Gracies JM, Esquenazi A, Brashear A, et al. Efficacy and safety of abobotulinumtoxinA in spastic lower limb. *Neurology* 2017; 89:2245-2253.

[7] Wissel J, Bensmail D, Ferreira JJ, et al. Safety and efficacy of incobotulinumtoxinA doses up to 800 U in limb spasticity: the TOWER study. *Neurology* 2017; 88:1321-1328.

Table 6: Adverse events in the submitted trials of Xeomin

	3098			3002			TOWER
	DB Phase		OLE	DB Phase		OLE	Open Label
	Xeomin N = 104	Placebo N = 104	N = 202	Xeomin N = 144	Placebo N = 145	N = 269	N = 155
Patients with any AE, n (%)	50 (48.1%)	51 (49.0%)	131 (65%)	41 (28.5%)	42 (29%)	121 (45%)	NR
Any SAE, n (%)	4 (4%)	1 (1%)	12 (6%)	6 (4%)	5 (3%)	22 (8%)	17 (11%)
Discontinuation due to AE, n (%)	1 (1%)	2 (2%)	4 (3%)	7 (5%)	2 (1.5%)	14 (5%)	5 (3%)
AESI, n (%)	5 (5%)	4 (4%)	12 (6%)	6 (4%)	3 (2%)	11 (4%)	19 (12.3%)

Source: Table 65, p194, Table 66, p195, 3098 CSR; Table 52, p143, Table 53, p145, 3002 CSR; Wissel, 2017, Table 2.
AESI = adverse event of special interest.

6.33 Adverse events consistent with effects of Xeomin beyond the target muscles were relatively common, but none were serious, and causation in any individual case is uncertain.

6.34 Adverse events as reported in the Botox trials used for the indirect treatment comparison and in the Dysport trial (Gracies, 2017) are shown in Table 7.

Table 7: Adverse events in the trials of Botox

	Botox Trials				**Dysport Trial**		
	REFLEX		**512**		**Gracies, 2017**		
	Botox N = 233	Placebo N = 235	Botox N = 58	Placebo N = 62	Dysport 1000 U N = 127	Dysport 1500 U N = 128	Placebo N = 130
Patients with any AE, n (%)	95 (41.1%)	80 (34.3%)	26 (45%)	27 (44%)	55 (43.3%)	52 (40.6%)	41 (31.5%)
Patients with any serious AE, n (%)	NR	NR	5 (9%)	1 (2%)	5 (4%)	5 (4%)	7 (5.4%)
AESI, n (%)	NR	NR	NR	NR	6 (5%)	13 (10%)	7 (5.4%)

Source: Wein et al, 2018, Table 4; Kaji et al, 2010, Table 4; Gracies, 2017, Table 3.
AE = adverse event; AESI = adverse event of special interest; NR = not reported.

Indirect Treatment Comparisons

Efficacy

6.35 The nominated non-inferiority margin of Xeomin versus Botox for MAS was 0.5 points at week 4. The differences in MAS scores versus placebo at this time point were -0.27 in both Xeomin and Botox trials, so this non-inferiority margin was too large. No non-inferiority margin for the proportion of responders was nominated.

6.36 All submitted indirect treatment comparisons inappropriately excluded the data from 3002.

6.37 The indirect mean difference (95% CI) in MAS at 4 weeks for Xeomin versus Botox was -0.002 (-0.23, 0.23). The lower bound of the 95% CI for the difference was within the nominated non-inferiority margin, but this was uninformative because the non-inferiority margin was much larger than the effect size versus placebo.

6.38 The indirect comparison of treatment responders (defined as ≥1 point reduction in MAS) at 4 weeks reported only relative risk. The relative risk (95% CI) for Xeomin versus placebo using only the data from 3098 was 1.35 (1.01, 1.80) so inclusion of data

from 3002 may have resulted in the pooled relative risk of response with Xeomin not being statistically significant. The relative risk (95% CI) for Botox versus placebo was 1.48 (1.23, 1.77), and the indirect relative risk of Botox versus Xeomin was 1.10 (0.78, 1.54), but this result also would have been different if the data from 3002 had been included.

Safety

6.39 The indirect treatment comparison of safety was confined to total adverse events and serious adverse events in 3098 and 512 only. There was no difference between Xeomin and Botox.

Benefits/harms

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

Clinical claim

6.41 The submission described Xeomin as non-inferior in terms of effectiveness compared to Botox. The evaluation considered this claim was not adequately supported because of two randomised placebo-controlled trials submitted, the larger found no difference between Xeomin and placebo, and this trial was omitted from the indirect treatment comparison. Xeomin was not superior to placebo in either trial in functional outcomes, which PBAC has previously determined to be essential for clinical significance.

6.42 Whilst recognising the uncertainties associated with the comparison, 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).

6.43 The submission described Xeomin as non-inferior in terms of safety compared to Botox. The PBAC considered that this claim was reasonable.

Economic analysis

6.44 The submission presented a cost minimisation approach for the economic evaluation. The key components and assumptions used in the approach are shown in Table 8.

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

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence presented in Section 2, effectiveness is assumed to be non-inferior.
Therapeutic claim: safety	Based on evidence presented in Section 2, safety is assumed to be non-inferior.
Evidence base	{Direct comparison of proposed medicine and main comparator/indirect comparison of proposed medicine and main comparator}
Equi-effective doses	IncobotulinumtoxinA A 400units = botulinum toxin A 400units
Direct medicine costs	Costs of proposed medicine and comparator are equivalent, $1098.88 for the maximum dosage per patient per treatment cycle
Other costs or cost offsets	None

Source: Table 3.1.1, p74 of the submission.

6.45 The submission stated that the PBAC has previously considered that equi-effective doses should be based on the maximum dispensed quantities (Paragraph 7.3, Dysport PSD, July 2019) and therefore the equi-effective doses of incobotulinumtoxinA (Xeomin) and onabotulinumtoxinA (Botox) would be 400 U = 400 U. This was consistent with the previously approved dose relativities for the products.

6.46 Appropriately no additional costs were included in the analysis. The results of the CMA are shown in Table 9.

Table 9: Results of the cost minimisation approach

Molecule	Brand	Maximum Dose Dispensed	Maximum qty per pack	Packs per treatment cycle	DPMQ	Cost per treatment cycle	Difference
IncobotulinumtoxinA	Xeomin	400	400	1	$1,098.88	$1,098.88	$0.00
Botulinum toxin type A	Botox	400	400	1	$1,098.88	$1,098.88	

Source: Table 3.1.1, p 75 of the submission.

6.47 The published price (DPMQ) of (Dysport) for a treatment cycle of 1500 units for the lower limb spasticity indication is $1190.83. The equi-effective doses of Dysport and Botox for the lower limb indication were considered by the PBAC to be 3.75U Dysport = 1U Botox. (Paragraph 7.3, Dysport PSD, July 2019).

Drug cost/patient/treatment cycle

6.48 The drug cost per patient per treatment cycle for the maximum dosage was $1098.88.

Estimated PBS usage & financial implications

6.49 This submission was not considered by DUSC.

6.50 The submission presented a market share approach to estimate the utilisation and cost of listing Xeomin for the treatment of low limb spasticity in adults following an acute event. The key inputs and assumptions used in the analysis are shown in Table 10.

Table 10: Key inputs for financial estimates

Parameter	Value applied and source	Comment
PBS Services for Botox and Dysport	http://medicarestatistics.humanservices.gov.au/statistics/pbs_item.jsp Item codes for all botulinum toxin items for the treatment of moderate to severe lower limb spasticity in adults following an acute event.	
Annual growth rate of botulinum toxin market	http://medicarestatistics.humanservices.gov.au/statistics/pbs_item.jsp 20.7%	Reasonable
Rate of displacement by Xeomin	Sponsor assumption year / proportion 2026 / [redacted]% 2027 / [redacted]% 2028 / [redacted]% 2029 / [redacted]% 2030 / [redacted]% 2031 / [redacted]%	Could not be independently verified.
Dose equivalence	Xeomin and Botox are equivalent on a unit per patient basis; The PBAC listed Dysport against Botox at a 3.75:1 ratio. https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2019-07/files/clostridium-botulinum-toxin-psd-july-2019.pdf	As per previous PBAC considerations
Drug prices (DPMQ)	Xeomin: Effective price: $1098.88 Botox (PBS Code 11751L): $1098.88 Dysport 300 units (PBS Code 11831Q): $1190.83 Dysport 500 units (PBS Code 11857C): $1270.98	Correct as of Nov 19 2025
Average patient copayments	PBS: $21.67 RPBS: $6.25	Calculated from PBS service volumes for the requested indication from 2024 data.
MBS item, injection fee.	MBS item 18365, treatment of moderate to severe spasticity of the lower limb following an acute event in adults, $145.65	Assumes that Xeomin will replace Dysport with a reduction in injections – may be reasonable

Source: Tables 4.2.2, 4.2.4, 4.6.2 and accompanying text, pp77-79, p84 of the submission.

6.51 The annual growth rate of the market for botulinum toxin for this indication was appropriately calculated from the PBS Services data for the period 2021-2024, but was substantially higher than that presented in the July 2025 submission for upper limb spasticity and equinus deformity due to cerebral palsy, which was 4.1%.

6.52 The total estimated financial impact of listing Xeomin is shown in Table 11 (using the effective price).

Table 11: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Estimated financial implications of Xeomin						
Cost to PBS/RPBS less copayments	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Estimated financial implications for Botox and Dysport						
Botox, 11751L	-[redacted][1]	-[redacted][1]	-[redacted][2]	-[redacted][2]	-[redacted][2]	-[redacted][2]
Dysport, 11831Q	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]
Dysport, 11857C	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]
Total change in scripts	-[redacted][1]	-[redacted][1]	-[redacted][2]	-[redacted][2]	-[redacted][2]	-[redacted][2]
Cost to PBS/RPBS less copayments	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]
Net financial implications						
Net cost to PBS/RPBS	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]
Net cost to MBS	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]
Net cost to PBS/RPBS/MBS	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]

Source: Tables 4.3.3, 4.3.5, 4.4.1, 4.4.2, 4.6.3, 4.6.4 pp 81-85 of the submission.

The redacted values correspond to the following ranges:

[1] *< 500*

[2] *500 to < 5,000*

[3] *$0 to < $10 million*

[4] *net cost saving*

6.53 The total cost to the PBS/RPBS of listing Xeomin was estimated to be $0 to < $10 million in Year 6, and a net save of -$0 to < $10 million in the first 6 years of listing.

6.54 The submission presented a sensitivity analysis varying the rate of Xeomin displacing other botulinum toxin products by +/- [redacted]%. The estimates of financial impact remained cost saving for the PBS under both scenarios.

Quality Use of Medicines

6.55 The submission presented a brief list of activities planned to support quality use of medicines with respect to use of Xeomin in all indications including the new indication. These were:

- 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 Xeomin.

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 lower limb in adults following stroke, traumatic brain injury, or spinal cord injury. 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 noted that a submission to the MSAC has been made to amend existing MBS item code 18360 to include incobotulinumtoxinA for the lower limb indication. The PBAC considered that changes to the PBS and MBS listing would have to be implemented on the same date.

7.3 The PBAC advised that the Xeomin® restriction should be consistent with the current Botox® and Dysport® restrictions for lower limb spasticity following an acute event.

7.4 The PBAC considered that the nominated comparator of Botox® was appropriate. The PBAC considered that Dysport® was also an alternative therapy. The PBAC recalled it had previously advised that Botox®, Dysport® and Xeomin® should be treated as interchangeable on an individual patient basis (Paragraph 6.15, Xeomin PSD, November 2019 PBAC Meeting).

7.5 The PBAC noted there were no direct head-to-head trials comparing Xeomin® and Botox® for lower limb spasticity and that the submission was based on an indirect treatment comparison with placebo as the common comparator, using one pivotal trial of Xeomin® (Study 3098) and 2 trials of Botox® (REFLEX and Trial 512). The PBAC also noted that another randomised controlled trial of Xeomin® for the treatment of lower limb spasticity has been completed (Study 3002) but the efficacy data was not included. The pre-PBAC response argued that Study 3002 was excluded for methodological reasons.

7.6 The PBAC recalled it had previously accepted that a one-point improvement in Modified Ashworth Score (MAS) associated with functional improvement would be a reasonable minimum clinically important difference. The PBAC noted there was a consistent but modest difference between Xeomin® and placebo in the proportions of patients in 3098 achieving a 1-point or 2-point change in Modified Ashworth Score (MAS), which was statistically significant at weeks 4, 6 and 8.

7.7 The PBAC noted that in 3098, there was no effect of Xeomin® on any functional outcome, so the effect of Xeomin® versus placebo was less than the minimum clinically important difference. The pre-PBAC response acknowledged this limitation but stated that it also applies to Botox® and Dysport®. The pre-PBAC identified (as did the evaluation) that REFLEX reported no difference between Botox and placebo in Clinical Global Impression (CGI) scores at 12 weeks or for walking speed at any time.

A trial of broadly similar design using Dysport® produced similar results. The PBAC recalled its previous recommendations for both Botox® (March 2019) and Dysport® (July 2019) for lower limb spasticity despite these limitations.

7.8 With respect to the indirect treatment comparison, the indirect mean difference (95% CI) in MAS at 4 weeks for Xeomin versus Botox® was -0.002 (-0.23, 0.23). The lower bound of the 95% CI for the difference was within the nominated non-inferiority margin (0.5), though the PBAC noted that the evaluation considered this margin to be too large as the differences in MAS scores versus placebo at this time point were -0.27 in the Xeomin and Botox trials.

7.9 The PBAC acknowledged the limitations of the comparison but considered that overall, the claim of non-inferior effectiveness and safety to Botox® was likely 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).

7.10 The PBAC noted that the submission presented a cost-minimisation approach between Xeomin® and Botox®. The PBAC advised that Xeomin® should be listed on a cost-minimisation basis against the least costly alternative therapy (Botox® or Dysport®). The PBAC recalled it had previously considered that equi-effective doses should be based on the maximum dispensed quantities (Paragraph 7.3, Dysport PSD, July 2019). The PBAC also recalled it had considered the equi-effective doses of Dysport and Botox for the lower limb indication to be 3.75U Dysport = 1U Botox. (Paragraph 7.3, Dysport PSD, July 2019). The PBAC therefore advised the equi-effective doses to be Xeomin 1 U = Botox 1 U = Dysport 3.75 U.

7.11 The PBAC noted that the submission presented a market share approach to estimate the utilisation and cost of listing Xeomin for the treatment of low limb spasticity in adults following an acute event. The analysis included the substitution of Botox and Dysport. The PBAC also noted that the submission claimed that the price of Dysport is slightly higher than the expected price for Botox and Xeomin and, therefore, any displacement of Dysport by Xeomin will generate savings for the PBS. The PBAC considered this was reasonable.

7.12 The 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®, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health*

(Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022 for Pricing Pathway A were not met.

7.13 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 PBS item code for the indication 22543 Moderate to severe spasticity of the lower limb following an acute event 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					
Restriction type: ☒Authority Required (Streamlined) [new/existing code]					
Administrative Advice: The units used to express the potency of botulinum toxin preparations currently available for PBS subsidy are not equivalent.					
Caution: Contraindications to treatment include known sensitivity to botulinum toxin.					
Administrative Advice: Special Pricing Arrangements apply.					
Indication: Moderate to severe spasticity of the lower limb following an acute event					
Clinical criteria:					
The condition must be moderate to severe spasticity of the lower limb/s following stroke or other acute neurological event, defined as a Modified Ashworth Scale rating of 3 or more,					
AND					
Clinical criteria:					
The treatment must only be used as second line therapy when standard management has failed; OR					
The treatment must only be used as an adjunct to physical therapy					
AND					
Clinical criteria:					
The treatment must not continue if the patient does not respond (defined as not having had a decrease in spasticity rating of at least 1, using the Modified Ashworth Scale, in at least one joint) after two treatment periods (with any botulinum toxin type A)					
AND					
Clinical criteria:					
Patient must not have established severe contracture in the limb to be treated,					
AND					
Clinical criteria:					

	The treatment must not exceed a maximum of 4 treatment periods (with any botulinum toxin type A) per lower limb in the first year of treatment, and 2 treatment periods with any botulinum toxin type A) per lower limb each year thereafter.
	Treatment criteria:
	Must be treated by a neurologist; OR
	Must be treated by an orthopaedic surgeon; OR
	Must be treated by a rehabilitation specialist; OR
	Must be treated by a plastic surgeon; OR
	Must be treated by a geriatrician
	Population criteria:
	Patient must be at least 18 years of age.
	Administrative Advice: Standard management includes physiotherapy and/or oral spasticity agents.
	Administrative Advice: An acute event may be clinical external event that leads to upper motor neuron lesions resulting in spasticity for example stroke, traumatic brain injury, spinal cord injury, infection or hypoxia.

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.