6.09 BOTULINUM TOXIN TYPE A PURIFIED NEUROTOXIN COMPLEX, Lyophilised powder for injection, 100 units, BOTOX®, Allergan Australia Pty Limited

1 Purpose of Application

1.1 The minor submission requested an expansion of the current Section 100 Authority Required (STREAMLINED) listing for botulinum toxin type A (herein known as BOTOX®) for the treatment of moderate to severe focal spasticity of the upper limb following a stroke to also include spasticity following acute events other than stroke.

1.2 An expansion of the same listing was recommended for clostridium botulinum type A toxin-haemagglutinin complex (herein known as Dysport®) at the March 2019 PBAC meeting and the change was made to the PBS on 1 October 2019.

2 Background

Registration status

2.1 BOTOX® was TGA registered in August 2003 for the treatment of focal spasticity in adults. Other approved indications include overactive bladder, urinary incontinence, prophylaxis of migraines, strabismus, focal spasticity of the lower limbs in children, focal spasticity of the upper limbs, spasmodic torticollis, blepharospasm, hemifacial spasm and glabellar lines.

2.2 The requested expansion of the PBS listing to include treatment of moderate to severe focal spasticity of the upper limb following any acute event is within the TGA approved indication for focal spasticity in adults.

2.3 BOTOX® is currently listed on the PBS as a Section 100 - Botulinum Toxin Program, Authority Required (STREAMLINED) listing for moderate to severe focal spasticity of the upper limb following a stroke.

Previous PBAC considerations

2.4 The PBAC recommended BOTOX® for the treatment of upper limb spasticity following a stroke in July 2008 on a cost-minimisation basis compared with Dysport®.

2.5 The PBAC recommended an extension of the PBS listing of Dysport® from upper limb spasticity following a stroke to upper limb spasticity following an acute event in March 2019.

2.6 The PBAC also considered a minor submission to extend the listing of Xeomin® for the treatment of upper limb spasticity at its November 2019 meeting (refer to item 6.12).

2.7 The PBAC recommended BOTOX® for the treatment of moderate to severe spasticity of the lower limb following an acute event in March 2019 (paragraph 5.2, BOTOX® Public Summary Document (PSD), March 2019).

For more detail on PBAC's view, see section 6 PBAC outcome.

3 Requested listing

The submission requested three amendments to the PBS criteria of the existing PBS listing for BOTOX®:

(i) Removal of the time limitation for first injection of post-stroke upper limb spasticity. The sponsor noted that the PBAC had previously determined that the timing of the onset of treatment should be at the discretion of the physician, that this was supported by the Rehabilitation Medicine Society of Australia and New Zealand (paragraph 2.4, Dysport® PSD, November 2018) and that this was consistent with the recommendation made by the PBAC in March 2019 for BOTOX® in lower limb spasticity;

(ii) Removal of the lifetime treatment limit of four treatment periods and replacement with annual limits as suggested by the PBAC in previous considerations of botulinum toxin in upper and lower limb focal spasticity; and

(iii) To include treatment of spasticity due to a range of acute aetiologies.

3.1 The PBAC noted that the amendments requested are relevant to Authority code 5220, which falls under PBS item 10999X.

3.2 The minor submission requested a special pricing arrangement (SPA) to achieve parity with the approved ex-manufacturer effective prices (AEMP) of Dysport®.

3.3 Changes to the current restriction proposed by the sponsor are in bold.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
BOTULINUM TOXIN TYPE A 100 units injection, 1 vial	4	0	Published: Public: $1,349.96 Private: $1,397.35 Effective: To be determined	BOTOX® Allergan

Category/Program:	Section 100 – Botulinum Toxin Program
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Severity:	Moderate to severe
Condition:	Spasticity of the upper limb following **~~a stroke~~ an acute event**
PBS Indication:	Moderate to severe spasticity of the upper limb following **~~a stroke~~ an acute event**
Restriction Level:	☒ Streamlined

Clinical criteria:	The condition must be moderate to severe spasticity of the upper limb/s following **an acute event** ~~**stroke**~~, defined as a Modified Ashworth Scale rating of 3 or more, AND ~~**The treatment must not be initiated until three months post-stroke,**~~ ~~**AND**~~ 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 greater than 1, using the Modified Ashworth Scale, in at least one joint) after two treatment periods **(with any botulinum toxin type A** ~~**total BOTOX, Dysport, and Xeomin),**~~ AND **The treatment must not exceed a maximum of 4 treatment periods (with any botulinum toxin type A) per upper limb in the first year of treatment, and 2 treatment periods (with any botulinum toxin type A) per upper limb each year thereafter.** ~~**The treatment must not exceed 4 treatment periods (total BOTOX, Dysport, and Xeomin) per upper limb per lifetime**~~ AND Patient must not have established severe contracture in the limb to be treated.
Population criteria:	Patient must be aged 18 years or older.
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.
Prescriber Instructions:	~~**The date of the stroke must be documented in the patient's medical records when treatment is initiated.**~~ Standard management includes physiotherapy and/or oral ~~**anti-**~~spasticity agents. ~~**The first year of treatment is defined as the year commencing on date of the first treatment on or after <DATE>.**~~
Administrative Advice:	The units used to express the potency of botulinum toxin preparations currently available for PBS subsidy are not equivalent. An acute event may be a clinical or external event that leads to upper motor neuron lesions resulting in spasticity for example, these may be stroke, traumatic brain injury, spinal cord injury, infection or hypoxia. Special Pricing Arrangements apply.
Cautions:	Contraindications to treatment include known sensitivity to botulinum toxin.

Category/Program:	*Section 100 – Botulinum Toxin Program*
Prescriber type:	☐ *Dental* ☒ *Medical Practitioners* ☐ *Nurse practitioners* ☐ *Optometrists* ☐ *Midwives*
Severity:	*Moderate to severe*
Condition:	*Spasticity of the upper limb following an acute event*
PBS Indication:	*Moderate to severe spasticity of the upper limb following an acute event*
Treatment phase:	*Grandfathered treatment*
Restriction Level:	☒ *Streamlined*

Clinical criteria:	*Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to [PBS listing date],* *AND* *The condition must have been moderate to severe spasticity of the upper limb/s following an acute event, defined as a Modified Ashworth Scale rating of 3 or more prior to commencing non-PBS subsidised treatment,* *AND* *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 did not respond (defined as not having had a decrease in spasticity rating greater than 1, using the Modified Ashworth Scale, in at least one joint) after two treatment periods (with any botulinum toxin type A),* *AND* *The treatment must not exceed a maximum of 4 treatment periods (with any botulinum toxin type A) per upper limb in the first year of treatment, and 2 treatment periods (with any botulinum toxin type A) per upper limb each year thereafter,* *AND* *Patient must not have established severe contracture in the limb to be treated.*
Population criteria:	*Patient must be aged 18 years or older.*
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.*
Prescriber Instructions:	*Standard management includes physiotherapy and/or oral spasticity agents.*
Administrative Advice:	*The units used to express the potency of botulinum toxin preparations currently available for PBS subsidy are not equivalent.* *An acute event may be a clinical or external event that leads to upper motor neuron lesions resulting in spasticity for example, these may be stroke, traumatic brain injury, spinal cord injury, infection or hypoxia.* *Special Pricing Arrangements apply.*
Cautions:	*Contraindications to treatment include known sensitivity to botulinum toxin.*

For more detail on PBAC's view, see section 6 PBAC outcome.

4 Comparator

4.1 The minor submission nominated Dysport® as the main comparator. This was appropriate as BOTOX® and Dysport® are used in the same place in the clinical management algorithm.

For more detail on PBAC's view, see section 6 PBAC outcome.

5 Consideration of the evidence

Sponsor hearing

5.1 There was no hearing for this item as it was a minor submission.

Consumer comments

5.2 The PBAC noted and welcomed the input from one individual for this item. The comment briefly described the difficulty of living with spasticity.

Clinical trials

5.3 In July 2008 the PBAC recommended BOTOX® for the treatment of upper limb spasticity following a stroke based on an indirect meta-analyses of five randomised trials of BOTOX® and six trials of Dysport® in the upper limb. Placebo was the common comparator. The meta-analyses were based on mean change in Ashworth Scale (AS) score in the wrist, elbow and finger flexor muscles in the BOTOX® trials and the mean change in Modified Ashworth Scale (MAS) scores in the Dysport® trials.

5.4 This minor submission was based on the evidence of six small, randomised trials which were considered by the PBAC as part of the sponsor's response to the July 2018 proposal from the RMSANZ (Item 12.03). The six trials, which included patients with spasticity due to a broad range of aetiologies, were:

(i) Fietzek 2014 (N = 52): cerebrally lesioned by stroke, hypoxic encephalopathy or traumatic brain injury;

(ii) Grazko 1995 (N = 12): a range of diagnoses;

(iii) Richardson 2000 (N = 52): cerebrovascular accidents, head injury, incomplete spinal cord injury, tumour, cerebral palsy or anoxic episodes;

(iv) Simpson 2009 (N = 60): post stroke or traumatic brain injury;

(v) Snow 1990 (N = 9): multiple sclerosis; and

(vi) Verplancke 2005 (N = 35): severe brain injury.

5.5 A summary of the trial characteristics and results is provided below.

Table 1: Summary of the BOTOX clinical trial characteristics and results

Trial ID	Design	Interventions	Population	Main outcomes/Results
Fietzek 2014	SC, R, DB, placebo-controlled trial with OL extension (N = 52)	BOTOX or placebo; total dose of 230U	Mostly severely disabled patients with unilateral or bilateral pes equinovarus (MAS ≥ +1) who were cerebrally lesioned by stroke, hypoxic encephalopathy or TBI within 12 weeks prior	MAS score Results: Patients who received BOTOX treatment significantly improved during the course of the first 12 weeks; MAS was reduced by 0.6 points ($p < 0.01$). The placebo-treated group did not show any significant change during the same period. At week 12 there was a significant difference of spastic muscle tone in the two treatment groups ($p < 0.01$). *TBI patients were not analysed separately.

Trial ID	Design	Interventions	Population	Main outcomes/Results
Grazko 1995	R, DB, placebo-controlled crossover trial (N = 12)	BOTOX or placebo; dose range was 25-250U	Patients with spasticity aged 12-81 years (N=12, n=8 with lower limb spasticity) due to range of diagnoses or rigidity (N=8)	AS score; Spasm frequency scale; Assessment of rigidity. Results: For 7 patients, the mean AS score at baseline was 3.6 (SD = 0.5; range 3-4) and this was reduced to 1.4 (SD = 0.5; range 1-2) at follow-up, a mean change of 2.1 (SD = 0.4; range 2-3). *TBI patients not assessed separately
Richardson 2000	R, DB, placebo controlled, PG trial (N = 52)	BOTOX or placebo was injected with EMG guidance. Doses were guided by clinical experience.	Patients with moderate to severe spasticity in focal muscle groups (upper or lower limbs) with a poor response to conventional physical and medical treatment Diagnoses included cerebrovascular accidents (23), head injury (12), incomplete SCI (6) tumour (5), cerebral palsy (3), and anoxic episodes (3).	AS score; Range of movement; Timed 10 metre walk; The Rivermead motor assessment. Results: AS: The aggregate outcome score (total of weeks 3, 6, 9 and 12) showed that the active treatment group had significantly better scores than the placebo group ($p < 0.02$). The range of movement improvement was significantly better for the BOTOX than for the placebo group ($p < 0.03$). For both groups there was a significant improvement in scores across time that occurred between baseline and 3 weeks.
Simpson 2009	MC, R, PG, DB (N = 60)	BOTOX (100-500U) + oral PBO vs IM PBO + tizanidine (2-36 mg/day) vs. IM PBO + oral PBO	Patients with upper limb focal spasticity ≥ 3 months post stroke (82%) or TBI (n=11) (18%)	Primary Change from baseline in wrist MAS score at 6 weeks. Results: BOTOX produced a greater reduction in wrist flexor tone than tizanidine or placebo at Week 3 and Week 6. *TBI patients not assessed separately
Snow 1990	R, DB, placebo controlled, cross-over study (N=10)	BOTOX 400U or placebo, in adductor muscles	Chair or bed-bound patients with chronic stable multiple sclerosis and adductor spasticity	Spasticity score Results: At 6 weeks following treatment there was a significant reduction in the spasticity score (7.9±4.87 to 4.7±4.31, p=0.009) and this was significantly better than the change following placebo treatment (6.8±5.26 to 7.1±4.77, p=0.009 for botulinum toxin vs. placebo.
Verplancke 2005	R, DB placebo controlled trial (N = 35)	Current physical treatment, casting plus placebo injections, or casting plus with BOTOX injections	Patients with severe brain injury, screened within 4 days of hospital admission, unable to achieve 3° of passive ankle dorsiflexion	MAS Results: The MAS scores were analysed as paired comparisons of MAS at entry and exit from the study. In the actively treated group (casting with BOTOX or saline injections), there was a statistically significant decrease of >1 point but by only 0.3 in controls, which was not significant.

AS = Ashworth Scale; DB = double-blind; EMG = electromyography; IM = intramuscular; MAS = Modified Ashworth Scale; MC = multi-centre; OL = open label; PBO = placebo; PG = parallel group; R = randomised; SC = single-centre; SCI = spinal cord injury; SD = standard deviation; TBI = traumatic brain injury

Source: Table 2.5-1, p40 of the minor submission

5.6 For the use of Dysport® in the treatment of upper limb focal spasticity following any acute event, the minor submission considered Study 145 (previously considered by the PBAC in November 2018). In Study 145 90% of patients had spasticity post-stroke, with approximately 10% suffering from spasticity due to a traumatic brain injury.

5.7 The PBAC considered the studies demonstrated varying levels of improvement versus placebo. The PBAC noted that it was not feasible to conduct an indirect comparison between BOTOX® and Dysport® due to small patient numbers and varying patient and trial characteristics.

5.8 The PBAC has 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 acute events was reasonable and biologically plausible (paragraph 5.2, Botox® PSD, March 2019; paragraph 7.2, Dysport® PSD, July 2019).

Clinical Claim

5.9 The clinical claim was that for patients with moderate to severe focal spasticity of the upper limb following an acute event, BOTOX® is non-inferior to Dysport® in terms of efficacy and safety.

5.10 The minor submission noted that the PBAC has previously considered that BOTOX was no worse in terms of effectiveness and had similar toxicity to Dysport in post-stroke upper limb spasticity (Section 9, BOTOX® PSD, July 2008).

5.11 The PBAC considered that the claim that BOTOX® was non-inferior to Dysport® in terms of comparative efficacy and safety following an acute event was likely to be reasonable given the established interchangeability in post-stroke upper limb focal spasticity.

Economic analysis

5.12 The minor submission presented a cost-minimisation analysis of BOTOX® compared with Dysport®.

5.13 The equi-effective doses were estimated in the minor submission as:

BOTOX® 229U = Dysport® 989U; or

BOTOX® 1U = Dysport® 4.3U

5.14 This relativity was based on the previous PBAC recommendation in July 2008.

Table 2: Equi-effective doses and dose relativities of BOTOX® and Dysport® previously accepted by the PBAC for the upper limb spasticity indication

	PBAC meeting	Equi-effective doses	Dose relativities	Source
Botox® vs. Dysport®	July 2008	Botox® 229U per treatment course = Dysport® 989U per treatment course	1:4.3	Botox® PSD, July 2008

PBAC = Pharmaceutical Benefits Committee; PSD = Public Summary Document

5.15 However in July 2019, Dysport® for the treatment of lower limb spasticity following an acute event was recommended based on a cost minimisation analysis with Botox®, in which the PBAC considered that the equi-effective doses of Dysport® and Botox® should be based on the maximum dispensed quantities which would result in equivalent treatment costs per cycle, that is:

Dysport® 3.75U = Botox® 1U (i.e. Dysport® 1,500U = Botox® 400U)

5.16 In addition, the PBAC has previously considered that the extent to which the potential use of botulinum toxin in both the upper and lower limbs in the same patient would affect utilisation, cost effectiveness and the financial implications remained uncertain. The PBAC was therefore of the view that any pricing arrangement for these indications should take these uncertainties into account by implementing a single price across these conditions (paragraphs 5.9 and 5.10, Botox® PSD, March 2019; paragraph 7.17, Dysport® PSD, July 2019).

5.17 The maximum doses recommended in the approved Product Information leaflets and the maximum quantities approved on the PBS for upper and lower limb spasticity are outlined below.

Table 3: Maximum doses and PBS quantities of botulinum toxin in ULFS and LLFS

	Maximum PI dose	Maximum PBS quantity	Current/recommended/requested PBS listing	PBAC consideration
Dysport®	ULFS = 1,000U	300U x 4, or 500U x 2	Current PBS listing for ULFS after an acute event	Recommended March 2019
	LLFS = 1,500U	300U x 5, or 500U x 3	Recommended PBS listing for LLFS after an acute event	Recommended July 2019
Botox®	ULFS = 360U	100U x 4	Current/requested PBS listing for ULFS after a stroke/an acute event	Requested November 2019
	LLFS = 400U	100U x 4	Current PBS listing for LLFS after an acute event	Recommended March 2019
Xeomin®	ULFS = 500U	100U x 4	Current/requested PBS listing for ULFS after a stroke/an acute event	Requested November 2019
	LLFS = NR	-	-	-

LLFS = lower limb focal spasticity; NR = not reported; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PI = Product Information; ULFS = upper limb focal spasticity
Source: Compiled by the Secretariat

5.18 Therefore, based on the July 2019 PBAC recommendation that Dysport® 1,500U = Botox® 400U, and the fact that the maximum PBS quantity for Botox® in both the upper and lower limb restrictions is 400U, the PBAC was asked to consider if the equi-effective doses should be BOTOX® 400U = Dysport® 1,500U (i.e. BOTOX® 1U = Dysport® 3.75U). In the pre-PBAC response, the sponsor reiterated that the dose relativity should be BOTOX® 1U = Dysport® 4.32U based on the upper limb relativity determined in July 2008.

Estimated PBS usage & financial implications

5.19 The minor submission used a hybrid approach to estimate the financial impact listing BOTOX® on the PBS. The methodology incorporated a review of the existing PBS items

for upper limb spasticity following a stroke and forecast of market share for the next six years where a combination of epidemiological data and real-world data reflecting treated populations in Australia and overseas were used. It was assumed that 100% of BOTOX® prescriptions were offset by reduced use of other forms of botulinum toxin.

5.20 The minor submission estimated an increase in BOTOX® utilisation due to treatment of patients with acute aetiologies, other than stroke, to be an additional [redacted]%. This estimate was based on a small study conducted in movement disorder clinics in four states in Australia (N = 79) with upper limb spasticity regardless of disease or condition[1].

5.21 In the financial estimates, the minor submission assumed that all patients who met the continuation criteria after four cycles received two treatment cycles per year indefinitely. This was likely an overestimation, as data considered previously by the PBAC indicated that re-injection intervals tended to increase over time.

5.22 The table below summarises the estimated use and financial implications for the proposed BOTOX® PBS listing. The PBAC noted that the requested listing was cost-neutral to the PBS.

Table 4: Summary of estimated utilisation and the financial impact of extending the PBS restriction

	Year 1 2019	Year 2 2020	Year 3 2021	Year 4 2022	Year 5 2023	Year 6 2024
Estimated extent of BOTOX® use - prescriptions						
Current post-stroke use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated use, including other aetiologies[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS/RPBS, less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Offsets due to reduced use of other forms of botulinum toxin (Dysport®, Xeomin®)						
Reduction in prescriptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost offset to PBS/RPBS, less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net financial implications						
Net cost to PBS/RPBS	$0	$0	$0	$0	$0	$0

DPMQ = dispensed price for maximum quantity; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

[a] Assuming 4 prescriptions in Year 1 and 2 prescriptions per year thereafter, and a DPMQ of $[redacted] (private) and $[redacted] (public) for 300U Botox®.

Source: Table 4.5-1, p52 of the submission.

The redacted table shows that at Year 6, the estimated number of prescriptions was more than 10,000.

5.23 The minor submission also estimated no net impact to the MBS.

5.24 As a minor submission, the financial estimates have not been independently evaluated.

[1] Based on sponsor survey

Quality use of medicines

5.25 The minor submission noted that the exact dose and number of injection sites should be tailored to the individual based on the size, number and location of muscles involved, the severity of the spasticity, presence of local muscle weakness, and the patient response to previous treatment.

5.26 In addition, the units used to express the potency of BOTOX® and Dysport® are not equivalent and extreme caution is required if it is necessary to substitute one brand for another.

For more detail on PBAC's view, see section 6 PBAC outcome.

6 PBAC Outcome

6.1 The PBAC recommended an extension of the current Section 100 (Botulinum Toxin Program), Authority Required (STREAMLINED) listing for botulinum toxin (BOTOX®) for treatment of moderate to severe focal spasticity of the upper limb following a stroke, to also include spasticity following acute events other than stroke. The PBAC was satisfied that BOTOX® was non inferior to Dysport® in terms of comparative efficacy and safety.

6.2 The PBAC noted that the request to add additional acute aetiologies, including traumatic brain and spinal cord injuries, to the upper limb focal spasticity restriction was supported by the Rehabilitation Medicine Society of Australia and New Zealand (RMSANZ).

6.3 The PBAC noted that the proposed restriction was identical to that recommended in March 2019 for Dysport® for the same indication. The PBAC recalled that it had previously considered that it would be reasonable for future botulinum toxin restrictions to be consistent in terms of initiation and continuation criteria and lifetime limits (paragraph 5.11, Dysport® PSD, March 2019).

6.4 The PBAC considered that a grandfather restriction, identical to the current grandfather restriction for Dysport®, would be appropriate for patients already treated with BOTOX® if requested by the sponsor.

6.5 The PBAC considered that Dysport® was the appropriate comparator.

6.6 The PBAC noted that the basis of the minor submission was evidence from six small, randomised trials which included patients with spasticity due to a broad range of aetiologies and which were previously considered by the PBAC as part of the sponsor's response to the July 2018 proposal from the RMSANZ. The PBAC considered that the evidence was of a low quality and that small patient numbers and varying patient and trial characteristics meant it was not feasible to conduct an indirect comparison between BOTOX® and Dysport®. The PBAC noted that it had previously considered that, despite the lack of clinical trials in these populations, the request was reasonable and biologically plausible (paragraph 5.2, Botox® PSD, March 2019; paragraph 7.2,

Dysport® PSD, July 2019). Therefore, the PBAC considered that BOTOX® was likely to be non-inferior in terms of comparative efficacy and safety to Dysport® in patients with focal upper limb spasticity due to an acute event.

6.7 The PBAC noted that the minor submission presented a cost minimisation analysis between BOTOX® and Dysport® based on the equi-effective doses and dose relativities previously accepted for upper limb spasticity following a stroke in July 2008.

6.8 The PBAC considered that the equi-effective doses nominated in the minor resubmission (BOTOX® 1U = Dysport® 4.3U) were not appropriate due to:

- the lack of comparative data in upper limb spasticity following an acute event other than stroke;
- the potential use of BOTOX® in both the upper and lower limbs of the same patient. The PBAC recalled that it had previously recommended a single price across these indications to account for the resulting uncertainties in terms of utilisation and cost effectiveness (paragraphs 5.9 and 5.10, Botox® PSD, March 2019; paragraph 7.17, Dysport® PSD, July 2019); and
- the maximum dispensed quantity of BOTOX® for upper limb spasticity was 400U. In July 2019, in consideration of lower limb spasticity, the PBAC recommended that BOTOX® 400U was equivalent to Dysport® 1500U (i.e. BOTOX® 1U = Dysport® 3.75U).

6.9 Therefore, the PBAC considered that the equi-effective doses were:

BOTOX® 1U = Dysport® 3.75U

6.10 The PBAC, noting the financial estimates, considered that the extension of the listing for BOTOX® should be cost-neutral to the PBS. The PBAC noted the proposed Special Pricing Arrangement (SPA) and recommended that BOTOX® join the existing Dysport® Risk Sharing Arrangement (RSA) which consists of subsidisation caps beyond which 100% rebates are applied. The PBAC considered that the RSA helped to address the uncertain clinical benefit in patients with upper limb spasticity due to an acute event other than stroke and the lack of data pertaining to the requested changes to the restrictions (i.e. removal of the time limitation for the first injection, removal of the lifetime limit and changes to the maximum number of cycles in the first and subsequent years).

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

6.12 The PBAC noted that the Early Supply Rule cannot currently be applied to items in the Botulinum Toxin Program

6.13 The PBAC reaffirmed that BOTOX® remained unsuitable for prescribing by nurse practitioners.

6.14 The PBAC recalled that the different formulations of botulinum toxin are not currently considered equivalent for the purposes of substitution (i.e. 'a' flagged in the Schedule) under Section 101 (4AACD) of the National Health Act and considered this remained appropriate.

6.15 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.

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

Outcome:
Recommended

7 Recommended listing

7.1 Amend existing listing as follows:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
BOTULINUM TOXIN TYPE A 100 units injection, 1 vial	4	0	BOTOX®	Allergan

Category/Program:	Section 100 – Botulinum Toxin Program
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	Moderate to severe
Condition:	Spasticity of the upper limb following an acute event
PBS Indication:	Moderate to severe spasticity of the upper limb following an acute event
Restriction level:	☒Streamlined
Clinical criteria:	The condition must be moderate to severe spasticity of the upper limb/s following an acute event defined as a Modified Ashworth Scale rating of 3 or more, AND 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 greater than 1, using the Modified Ashworth Scale, in at least one joint) after two treatment periods (with any botulinum toxin type A) AND The treatment must not exceed a maximum of 4 treatment periods (with any botulinum toxin type A) per upper limb in the first year of treatment, and 2 treatment periods (with any botulinum toxin type A) per upper limb each year thereafter. AND Patient must not have established severe contracture in the limb to be treated.
Population criteria:	Patient must be aged 18 years or older.
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.
Prescriber Instructions:	Standard management includes physiotherapy and/or oral spasticity agents.
Administrative Advice:	The units used to express the potency of botulinum toxin preparations currently available for PBS subsidy are not equivalent. An acute event may be a clinical or external event that leads to upper motor neuron lesions resulting in spasticity for example stroke, traumatic brain injury, spinal cord injury, infection or hypoxia. Special Pricing Arrangements apply.
Cautions:	Contraindications to treatment include known sensitivity to botulinum toxin.

Category/Program:	Section 100 – Botulinum Toxin Program
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	Moderate to severe
Condition:	Spasticity of the upper limb following an acute event
PBS Indication:	Moderate to severe spasticity of the upper limb following an acute event
Treatment phase:	Grandfathered treatment
Restriction level:	☒Streamlined
Clinical criteria:	Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to [PBS listing date] AND The condition must have been moderate to severe spasticity of the upper limb/s following an acute event, defined as a Modified Ashworth Scale rating of 3 or more prior to commencing non-PBS subsidised treatment. AND 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 greater than 1, using the Modified Ashworth Scale, in at least one joint) after two treatment periods (with any botulinum toxin type A) AND The treatment must not exceed a maximum of 4 treatment periods (with any botulinum toxin type A) per upper limb in the first year of treatment, and 2 treatment periods (with any botulinum toxin type A) per upper limb each year thereafter. AND Patient must not have established severe contracture in the limb to be treated.
Population criteria:	Patient must be aged 18 years or older.
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.
Prescriber Instructions	Standard management includes physiotherapy and/or oral spasticity agents.
Administrative Advice:	The units used to express the potency of botulinum toxin preparations currently available for PBS subsidy are not equivalent. An acute event may be a clinical or external event that leads to upper motor neuron lesions resulting in spasticity for example stroke, traumatic brain injury, spinal cord injury, infection or hypoxia. Special Pricing Arrangements apply.
Cautions:	Contraindications to treatment include known sensitivity to botulinum toxin.

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

8 Context for Decision

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

9 Sponsor's Comment

The sponsor had no comment.