

7.14 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 resubmission sought to address the issues raised by the PBAC at its November 2018 meeting, when it deferred the application for botulinum toxin type A (herein referred to as BOTOX®) for the treatment of adult patients with moderate to severe lower limb focal spasticity following a stroke.
- 1.2 The resubmission also sought to broaden the requested population to include patients with moderate to severe lower limb focal spasticity due to acute central nervous system (CNS) injury, including stroke and other acute aetiologies including traumatic brain injury (TBI) and spinal cord injury (SCI).

2 Requested listing

- 2.1 The resubmission requested modified restrictions to those proposed in the November 2018, which incorporated a number of the suggestions made by the Secretariat and issues raised by the PBAC (Section 2, BOTOX Public Summary Document (PSD), November 2018) and included acute CNS injury aetiologies in addition to stroke.
- 2.2 The pre-PBAC Response included additional minor changes to the restriction, as indicated by italics and strikethrough below.

Name, Restriction, Manner of administration and form	Max. Qty. (units)	No. of Rpts	Dispensed Price for Max. Quantity	Proprietary Name and Manufacturer
BOTULINUM TOXIN TYPE A 100 units injection, 1 vial	4	0	Published: Public: \$1,349.96 Private: \$1,397.25	Allergan Australia Pty Limited

Effective:
Public: \$ [REDACTED]
Private: \$ [REDACTED]

Category / Program:	Section 100 – Botulinum Toxin Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity	Moderate to severe
Condition:	Lower limb spasticity following a stroke <i>or other acute neurological event</i>
Treatment phase	Initial and continuing treatment
PBS Indication:	Moderate to severe spasticity of the lower limb following a stroke, or other acute neurological event
Restriction Level / Method:	<input checked="" type="checkbox"/> Streamlined
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,

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Population criteria	<p>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 of a least 1, using the Modified Ashworth Scale, in at least one joint) after two treatment periods per lower limb, AND Patient must not have established severe contracture in the limb to be treated, AND <i>The treatment must not exceed a maximum of 4 treatment periods per lower limb in the first year of treatment, and 2 treatment periods per lower limb each year thereafter.</i> Patient must be aged 18 years or older.</p>
Treatment criteria:	<p>Must be treated by a neurologist; OR Must be treated by an orthopaedic surgeon; OR Must be treated by a rehabilitation specialist <i>rehabilitation physician</i>; OR Must be treated by a plastic surgeon; OR Must be treated by a geriatrician.</p>
Prescribing instructions Administrative Note	<p>Standard management includes physiotherapy and/or oral <i>anti</i>-spasticity agents.</p> <p>The units used to express the potency of botulinum toxin preparations currently available for PBS subsidy are not equivalent. <i>Special Pricing Arrangements apply.</i></p>
Caution	Contraindications to treatment include known sensitivity to botulinum toxin.
Category / Program:	Section 100 – Botulinum Toxin Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity	Moderate to severe
Condition:	Lower limb spasticity following a stroke <i>or other acute neurological event</i>
Treatment phase: PBS Indication: Restriction Level / Method:	<p>Initial and continuing treatment – grandfathered patients Moderate to severe spasticity of the lower limb following a stroke, or other acute neurological event <input checked="" type="checkbox"/>Streamlined</p>
Clinical criteria:	<p>Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to <DATE>, 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 Patient must not have established severe contracture in the limb to be treated, AND <i>The treatment must not exceed a maximum of 4 treatment periods per lower limb in the first year of treatment, and 2 treatment periods per lower limb each year thereafter.</i></p>
Population criteria	Patient must be aged 18 years or older.
Treatment criteria:	<p>Must be treated by a neurologist; OR Must be treated by an orthopaedic surgeon; OR Must be treated by a rehabilitation specialist <i>rehabilitation physician</i>; OR Must be treated by a plastic surgeon; OR Must be treated by a geriatrician.</p>
Prescribing instructions Administrative Note	<p>Standard management includes physiotherapy and/or oral <i>anti</i>-spasticity agents.</p> <p><i>The units used to express the potency of botulinum toxin preparations currently available for PBS subsidy are not equivalent.</i></p>

Caution

Special Pricing Arrangements apply.
Contraindications to treatment include known sensitivity to botulinum toxin.

2.3 The PBAC noted that the resubmission accepted the majority of the comments and suggestions made during the evaluation of the November 2018 submission.

For more detail on PBAC's view, see section 5 PBAC outcome.

3 Background

3.1 The PBAC considered and deferred a major submission seeking reimbursement for BOTOX® for the treatment of lower limb focal spasticity following stroke at its November 2018 meeting, on the basis of outstanding issues with the proposed listing, economic model and requested price.

3.2 The PBAC previously considered (prior to its consideration in November 2018) a submission for lower limb focal spasticity post-stroke in July 2008 and submissions prior.

3.3 In its consideration of the submission in November 2018, the PBAC provided the following advice (BOTOX® PSD, November 2018):

- The PBAC noted the clinical need in the proposed population and acknowledged that, for some patients, a clinically meaningful response defined by an improvement in the Modified Ashworth Scale (MAS) of at least one was achieved, and that improvements in MAS were accompanied by other functional improvements (paragraph 7.2).
- The PBAC considered that there was a lack of comparative evidence beyond the first injection and insufficient evidence to inform dosing intervals or the benefit of continuing therapy, particularly beyond the first year of treatment. The PBAC also noted the limited data for the treatment of spasticity other than that causing plantar flexion of the ankle or equinovarus foot deformity (paragraph 7.4).
- The PBAC considered that standard of care/placebo was the appropriate comparator (paragraph 7.5).
- The PBAC considered that the magnitude of the benefit of BOTOX® was small following the first cycle and, although comparative data were unavailable beyond the first cycle, the PBAC noted that longer term follow up as a single agent indicated continued responses in those who chose to continue with subsequent treatments (paragraph 7.9).
- The PBAC considered that BOTOX® was inferior in terms of safety compared to standard of care/placebo (paragraph 7.10).
- The PBAC considered there were issues with the economic model (see further discussion in the Economic Analysis section below) (paragraphs 7.12 and 7.13).

- The PBAC noted the advice from DUSC that utilisation estimates were likely reasonable, although were not without concerns of both under- and over-estimation of utilisation (paragraph 7.14).

4 Consideration of the evidence

Sponsor hearing

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

Consumer comments

4.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

4.3 No new clinical trials or clinical information were presented in the resubmission.

Clinical claim

4.4 Whilst the resubmission did not present new clinical information, the sponsor indicated it did not accept the PBAC position that BOTOX[®] was inferior in terms of safety compared to standard of care/placebo (paragraph 7.10, BOTOX[®] PSD, November 2018). The sponsor reiterated its argument that a clinical claim of non-inferior safety versus placebo was supported by the evidence presented in the previous submission. The PBAC noted that there was no change to the information provided in the previous submission.

Economic analysis

4.5 The minor resubmission provided a new base case and sensitivity analyses based on advice provided by the PBAC when considered at the November 2018 meeting. Changes to the economic model requested by the PBAC (BOTOX[®] PSD, November 2018) and presented in the resubmission included:

- A sensitivity analysis using an alternative response criteria (as defined by a change in Modified Ashworth Scale (MAS) score of > one point) (paragraph 7.12);
- A stepped economic analysis with a re-specified base case with the following parameters the PBAC considered a more appropriate base case would (paragraph 7.13):
 - incorporate the discontinuations observed in the open label phase of the REFLEX trial (18%) as non-responders;
 - apply a frequency of retreatment that was consistent with that suggested by the PBAC and with clinical input, i.e. four treatments in the first year, followed by two treatments in subsequent years;
 - apply the non-responder utility value to the last-line health state, as

recommended by ESC; and

- result in an incremental cost-effectiveness ratio (ICER) of approximately \$15,000 to \$45,000 per quality adjusted life year (QALY).

4.6 The PBAC Secretariat validated the respecified economic model during the evaluation, and the impact of the model changes are presented below. The base case ICER (discounted) in the November 2018 submission was \$15,000/QALY to \$45,000/QALY.

Table 1: ICER – November 2018 submission

Outcome	BOTOX + SOC	SOC	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	2.4019	2.3102	0.0917
Incremental cost per QALY			\$ [REDACTED]

Source: Table 2.2-1 of the submission (Table 3-22 of the major submission, November 2018 PBAC)
 ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life year; SOC = standard of care

4.7 The resubmission stated that the proportion of patients in response at week 48 (79.6%) was consistent with, and slightly conservative to, the advice provided by the PBAC, which was to have 18% of patients as non-responders (i.e. 82% responders). The resubmission therefore made no further adjustment to the model to incorporate discontinuations in the open label phase.

4.8 The impact of applying a frequency of retreatment of four treatments in the first year, followed by two treatments in subsequent years increased the number of treatments from one to two in the fifth year of the model and is presented below.

Table 2: ICER - Revised frequency of re-treatment

Outcome	BOTOX + SOC	SOC	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	2.4019	2.3102	0.0918
Incremental cost per QALY			\$ [REDACTED]

Source: Table 2.2-4 of the resubmission. Rounded outcomes presented in table; ICER derived from non-rounded results.
 ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life year; SOC = standard of care

4.9 The resubmission argued the application of the non-responder utility value to the last-line health state was a conservative approach for the model. However, this was accepted by the sponsor, and the impact of applying the non-responder utility value (0.525) to the last line health state (previously 0.504) is presented in the table below.

Table 3: ICER - Revised utility weight for 'last-line' state

Outcome	BOTOX + SOC	SOC	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	2.4410	2.3884	0.0525
Incremental cost per QALY			\$ [REDACTED]

Source: Table 2.2-5 of the resubmission.
 ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life year; SOC = standard of care

4.10 Combining the above modifications to the base case gave the following re-specified base case economic model results.

Table 4: ICER - Revised frequency of re-treatment and utility weight for 'last-line' state

Outcome	BOTOX + SOC	SOC	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	2.4458	2.3933	0.0525
Incremental cost per QALY			\$ [REDACTED]

Source: Table 2.2-6 of the resubmission.

ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life year; SOC = standard of care

4.11 The resubmission provided an updated price offer of an effective approved ex-manufacturer price (AEMP) of \$ [REDACTED] per 100 unit vial, which gave a resultant ICER of less than \$15,000 per QALY.

Table 5: ICER - Re-specified base case, effective approved ex-manufacturer price of \$281.49/100 units

Outcome	BOTOX + SOC	SOC	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	2.4458	2.3933	0.0525
Incremental cost per QALY			\$ [REDACTED]

Source: Table 2.2-8 of the resubmission.

ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life year; SOC = standard of care

4.12 The resubmission also provided an update (using the new price) to earlier steps of the stepped economic analysis (Table 14, p28, BOTOX® PSD, November 2018) with the following results.

Table 6: Re-specified stepped economic analysis

Costs			Health outcomes			ICER – Mar 2019	ICER – Nov 2018
BOTOX + SOC	SOC	Increment	BOTOX + SOC	SOC	Increment		
Step 1: 12 week DB trial based CEA, % responders with ≥ 1-grade MAS response at any time							
\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	65.80%	51.50%	14.30%	\$ [REDACTED]/responder	\$ [REDACTED]/responder
Step 2: 24 weeks extended DB + OL based CEA, % responders with ≥ 1-grade MAS response at any time							
\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	89.60%	51.50%	38.10%	\$ [REDACTED]/responder	\$ [REDACTED]/responder
Step 3: CUA, 5-year Markov Cohort Model (discounted)							
\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	2.4458	2.3933	0.0525	\$ [REDACTED]/QALY	\$ [REDACTED]/QALY

Source: Table 2.2-9 of the resubmission

CEA = cost-effectiveness analysis; CUA = cost-utility analysis; DB = double-blind; ICER = incremental cost-effectiveness ratio; MAS = modified Ashworth Scale; OL = open-label; QALY = quality adjusted life year; SOC = standard of care

Drug cost/patient/cycle (400 units): Published = \$1,370.23; Effective = \$ [REDACTED]

4.13 Drug costs per patient per cycle were calculated using the AEMP published price (AEMP \$337.49/100 units) and the AEMP effective price (\$ [REDACTED]/100 units) for 400 units (1 treatment cycle) and weighted for proportional private hospital (43%) and public hospital (57%) use.

Estimated PBS usage & financial implications

4.14 The resubmission provided updated utilisation estimates to incorporate use of BOTOX® in lower limb focal spasticity due to acute aetiologies other than stroke. The

utilisation estimates for post-stroke patients were unchanged from the November 2018 submission. The DUSC considered that the November 2018 utilisation estimates were likely reasonable, although were not without concerns of both under- and over-estimation (paragraph 7.14, BOTOX[®] PSD, November 2018).

- 4.15 The utilisation of BOTOX[®] for lower limb spasticity due to other acute aetiologies was based on an Australian focal spasticity treatment survey that was completed by 12 doctors and presented in the March 2008 submission. The utilisation of BOTOX[®] in patients with spasticity due to aetiologies other than stroke was uncertain as the data-source was outdated.
- 4.16 In addition, the resubmission did not incorporate the revised maximum dose of four injections in the first year and two injections per year thereafter into the utilisation estimates.
- 4.17 As the resubmission requested a special pricing arrangement (SPA) to the original requested price for this indication, financial impact estimates were provided for both the published (\$337.49/100 units) and effective (\$ [REDACTED]/100 units) prices.
- 4.18 As per the original submission, the resubmission accounted for additional Medicare Benefits Schedule (MBS) costs associated with muscle location methods and administration costs in the financial estimates (MBS item 18360; 85% fee = \$106.15). The resubmission also accounted for additional costs associated with specialist follow-up consultations associated with BOTOX[®] injections (MBS item 116; 85% fee = 65.20) as per paragraph 6.63, BOTOX[®] PSD, November 2018.
- 4.19 The utilisation and financial estimates are presented below.

Table 7: Utilisation and financial estimates

	Year 1 (2019)	Year 2 (2020)	Year 3 (2021)	Year 4 (2022)	Year 5 (2023)	Year 6 (2024)
Number of vials dispensed						
Total vial numbers in LLFS post stroke	████	████	████	████	████	████
Total vial numbers in LLFS following other acute neurological event (TBI/SCI)	████	████	████	████	████	████
Total number of LLFS vials	████	████	████	████	████	████
Number of scripts dispensed						
Total script numbers in LLFS post stroke	████	████	████	████	████	████
Total script numbers in LLFS following other acute neurological event (TBI/SCI)	████	████	████	████	████	████
Total script numbers	████	████	████	████	████	████
Financial estimates at EFFECTIVE price¹ (minus average co-payment of \$15.40² per prescription)						
Cost to PBS	\$████	\$████	\$████	\$████	\$████	\$████
Cost to RPBS	\$████	\$████	\$████	\$████	\$████	\$████
Net PBS/RPBS cost	\$████	\$████	\$████	\$████	\$████	\$████
Net MBS cost	\$████	\$████	\$████	\$████	\$████	\$████
Net cost to health budget	\$████	\$████	\$████	\$████	\$████	\$████
Financial estimates at PUBLISHED price¹ (minus average co-payment of \$15.40² per prescription)						
Cost to PBS	\$████	\$████	\$████	\$████	\$████	\$████
Cost to RPBS	\$████	\$████	\$████	\$████	\$████	\$████
Net PBS/RPBS cost	\$████	\$████	\$████	\$████	\$████	\$████
Net MBS cost	\$████	\$████	\$████	\$████	\$████	\$████
Net cost to health budget	\$████	\$████	\$████	\$████	\$████	\$████
<i>November 2018 Net PBS/RPBS cost (i.e. stroke patients only)</i>	\$████	\$████	\$████	\$████	\$████	\$████
<i>November 2018 Net cost to health budget (i.e. stroke patients only)</i>	\$████	\$████	\$████	\$████	\$████	\$████

Source: Submission utilisation and financial estimates (Tables 3.4-1 – 3.4-6 of the resubmission) and Table 15, p29 of the November 2018 PBAC PSD

AEMP = approved ex-manufacturer price; DPMQ = dispensed price for maximum quantity; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

¹ DPMQ for private hospitals estimated during the evaluation based on the published AEMP of \$337.49/vial and effective AEMP of \$████/vial generated small discrepancies with the resubmission's values

² Average co-payment sourced from utilisation and financial estimates spreadsheet (Background and Assumptions) and based on value proposed during the evaluation of the major submission (Botox COM Table 4.1.1 pg. 121)

The redacted table shows that at Year 6, the estimated number of vials was 50,000 to 100,000 and the net cost to the PBS would be \$20 to \$30 million.

4.20 The resubmission presented a number of sensitivity analyses to the financial estimates, including:

- Application of an alternative growth curve to post-stroke upper limb spasticity (logarithmic curve) (SA #1). The base case assumed linear growth based on

historical data.

- 10% lower utilisation for all lower limb spasticity (SA #2a).
- 10% higher utilisation for all lower limb spasticity (SA #2b).
- Alternative utilisation assumptions for lower limb spasticity due to TBI and SCI derived from the ASPIRE study, which reported data from an international registry (SA #3). The base case derived utilisation from a 2008 Australian treatment survey of 12 doctors.
- A lower assumption of 3.47 vials per patient per treatment cycle (SA #4). The base case assumed 4 vials.

4.21 The results of these sensitivity analyses are presented in the table below.

Table 8: Net cost to PBS/RPBS (published price) - Sensitivity Analyses*

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Base Case	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
SA #1: application of alternative growth curve to ULS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
SA #2a: -10% utilisation	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
SA #2b: +10% utilisation	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
SA #3: alternate aetiology assumptions	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
SA #4: 3.47 vials/cycle	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Table 3.5-2 of the resubmission

MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; ULS = upper limb spasticity

* Sensitivity analyses based on PBS/RPBS costs only (non-inclusive of MBS costs)

4.22 More detailed results of the impact of the use of the alternative aetiology estimates for TBI and SCI (SA #3 above) are presented in the table below.

Table 9: Net cost to PBS/RPBS (published price) - Sensitivity Analyses, TBI and SCI*

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Traumatic Brain Injury						
Alternative TBI estimate (11%)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
TBI base case (29%)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Change from base	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
Spinal Cord Injury						
Alternative SCI estimate (10%)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
SCI base case (8%)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Change from base	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Table 3.5-3 of the resubmission

MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; SCI = spinal cord injury; TBI = traumatic brain injury

*Sensitivity analyses based on PBS/RPBS costs only (non-inclusive of MBS costs)

For more detail on PBAC's view, see section 5 PBAC outcome.

5 PBAC Outcome

5.1 The PBAC recommended the Section 100 (Botulinum Toxin Program), Authority Required (STREAMLINED) listing of botulinum toxin type A (BOTOX®) for focal

spasticity of the lower limb following stroke or other acute neurological event. The PBAC was satisfied that BOTOX[®] provided, for some patients, an improvement in efficacy over standard of care.

- 5.2 In November 2018, the PBAC considered that there was a clinical need for effective treatments for lower limb focal spasticity following stroke. The PBAC noted the request to add additional acute aetiologies, including traumatic brain and spinal cord injuries, to the requested population. The PBAC noted that this request was supported by the Rehabilitation Medicine Society of Australia and New Zealand (RMSANZ). The PBAC considered that, despite the lack of clinical trials in these populations, the request was reasonable and biologically plausible.
- 5.3 The PBAC considered the restriction as proposed by the sponsor in its pre-PBAC Response was reasonable, and incorporated the recommendations made in November 2018 related to condition eligibility, initiation and stopping rule criteria and the maximum number of treatment cycles per year.
- 5.4 The PBAC considered that a grandfather restriction may be appropriate for patients already treated with BOTOX[®] who meet response criteria, if requested by the sponsor.
- 5.5 The PBAC noted that no new clinical data were provided in the resubmission. The PBAC noted that the sponsor indicated that it did not accept the PBACs position that BOTOX[®] was inferior in terms of safety compared to standard of care. The PBAC considered that as no new safety information was provided its consideration that BOTOX[®] was inferior in term of safety compared to standard of care/placebo was unchanged.
- 5.6 The PBAC noted that the resubmission addressed the issues identified by the PBAC when considering the November 2018 economic analysis. The PBAC noted that the effective price reduction, requested through a Special Pricing Arrangement (SPA), achieved a resultant incremental cost-effectiveness ratio (ICER) of less than \$15,000 per QALY. This was within the range the PBAC considered appropriate at the November 2018 meeting. The PBAC considered that the lower ICER adequately addressed uncertainties regarding the inclusion of patients following an acute event other than stroke into the PBS population and in the data pertaining to the changed restriction (including removal of the lifetime limit and changes to the maximum number of cycles in the first and subsequent years).
- 5.7 The PBAC noted that SPAs are given effect through a deed made under Section 85E of the *National Health Act 1953* (Act) between the Minister (or his delegate) and the responsible person. The PBAC further noted that the Minister (or his delegate) has requested advice under section 101(3) of the Act as to whether BOTOX[®] meets criteria 1 and 2(a) of the Special Pricing Arrangement criteria when used for the treatment of moderate to severe focal spasticity of the lower limb following an acute event. In regards to criteria 1, the PBAC considered that BOTOX[®] generates a benefit for people with focal spasticity of the lower limb, and for criteria 2(a), that BOTOX[®] has been shown to have unique characteristics compared to standard of care/placebo in

improving limb function.

- 5.8 The PBAC recalled it had previously considered the utilisation and financial estimates, as advised by the Drug Utilisation Sub-Committee (DUSC), were likely to be reasonable for the post-stroke population. The PBAC noted the submission estimated that inclusion of patients with lower limb spasticity following an acute event other than stroke would increase the utilisation estimates by approximately █% and considered that although there were inherent uncertainties in the estimates for the other acute neurological event population as demonstrated by the sensitivity analyses, the estimates were reasonable.
- 5.9 The PBAC noted 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 financial implications remained uncertain.
- 5.10 The Committee was therefore of the view that any pricing arrangements for these indications should take these uncertainties into account, which could be achieved by implementing a █ across these conditions.
- 5.11 The PBAC considered it would be reasonable to ensure any future PBS restrictions for botulinum toxin for upper or lower limb focal spasticity are consistent in terms of initiation and continuation criteria and lifetime limits. Although the PBAC considered that there was no biologically plausible reason for response criteria (as defined by reduction in MAS score) to differ between upper and lower limb listings, it noted correspondence from RMSANZ that suggested that there were no major concerns with these not being the same.
- 5.12 The PBAC recalled and noted that the Early Supply Rule cannot currently be applied to items in the Botulinum Toxin Program.
- 5.13 The PBAC reaffirmed that BOTOX[®] remained unsuitable for prescribing by nurse practitioners.
- 5.14 The PBAC recalled that the different formulations of botulinum toxins 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.
- 5.15 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

Recommended listing

5.16 Add new item:

Name, Restriction, Manner of administration and form	Max. qty. (units)	No. of Rpts	Proprietary Name and Manufacturer
BOTULINUM TOXIN TYPE A 100 units injection, 1 vial	4	0	Botox® Allergan Australia Pty Limited

Category/Program:	Section 100 – Botulinum Toxin Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity	Moderate to severe
Condition:	Spasticity of the lower limb following an acute event
PBS Indication:	Moderate to severe spasticity of the lower limb following an acute event
Restriction Level/ Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	<p>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</p> <p>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</p> <p>The treatment must not continue if the patient does not respond (defined as not having had a decrease in spasticity rating of a least 1, using the Modified Ashworth Scale, in at least one joint) after two treatment periods (with any botulinum toxin type A), AND</p> <p>Patient must not have established severe contracture in the limb to be treated, AND</p> <p>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.</p>
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 physician; OR Must be treated by a plastic surgeon; OR Must be treated by a geriatrician.
Prescribing instructions	Standard management includes physiotherapy and/or oral spasticity agents.
Administrative note	The units used to express the potency of botulinum toxin preparations currently available for PBS subsidy are not equivalent. Special Pricing Arrangements apply.
Administrative advice	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.
Caution	Contraindications to treatment include known sensitivity to botulinum toxin.

Category/Program:	Section 100 – Botulinum Toxin Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity	Moderate to severe

Condition:	Spasticity of the lower limb following an acute event
Treatment phase:	Continuing treatment – grandfathered patients
PBS Indication:	Moderate to severe spasticity of the lower limb following an acute event
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	<p>Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to <DATE>, AND</p> <p>The condition must have been moderate to severe spasticity of the lower 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</p> <p>The treatment must only be used as second line therapy when standard management has failed; OR</p> <p>The treatment must only be used as an adjunct to physical therapy, AND</p> <p>The treatment must not continue if the patient did 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</p> <p>Patient must not have established severe contracture in the limb to be treated, AND</p> <p>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.</p>
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 physician; OR Must be treated by a plastic surgeon; OR Must be treated by a geriatrician.
Prescribing instructions	Standard management includes physiotherapy and/or oral anti-spasticity agents.
Administrative note	The units used to express the potency of botulinum toxin preparations currently available for PBS subsidy are not equivalent. Special Pricing Arrangements apply.
Administrative advice	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.
Caution	Contraindications to treatment include known sensitivity to botulinum toxin.

6 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

7 Sponsor's Comment

The sponsor had no comment.