7.03 CLOSTRIDIUM BOTULINUM TYPE A TOXIN – HAEMAGGLUTININ COMPLEX, Lyophilised powder for I.M. injection 300 units, 500 units, Dysport®, Ipsen Pty Ltd

1 Purpose of Application

1.1 The resubmission requested a Section 100 (Botulinum Toxin Program), Authority Required (STREAMLINED) listing for Clostridium botulinum type A toxin - haemagglutinin complex (herein known as Dysport®), for treatment of adult patients with moderate to severe spasticity of the lower limb following stroke. The requested population was amended in the Pre-Sub-Committee response (PSCR) to include patients with lower limb focal spasticity following an acute neurological event.

1.2 Dysport® is PBS listed for the treatment of upper limb spasticity following stroke and several other indications. At the March 2019 PBAC meeting the Dysport® listing for upper limb spasticity following a stroke was extended to include spasticity following an acute event (web outcome, Dysport®, March 2019).

1.3 This was the second submission for Dysport® for the treatment of lower limb focal spasticity (LLFS). The previous submission (November 2018) was for patients following any acute event including stroke and other aetiologies. The PBAC rejected the original submission at the November 2018 meeting based on uncertain clinical effectiveness, high and uncertain incremental cost-effectiveness ratio (ICER) which was based on flawed economic evaluation and uncertain financial estimates.

1.4 As with the previous submission, the requested listing was intended to address inconsistencies in available treatment for spasticity as outlined by the Rehabilitation Medicine Society of Australia and New Zealand (RMSANZ) position statement, 2017. In March 2019, the PBAC recommended Botox® formulation of botulinum toxin type A (BoNT) for the treatment of moderate to severe LLFS following stroke or other acute events (web outcome, Botox®, March 2019). The requested restriction for Dysport® was broadened in the PSCR to include patients with focal spasticity of the lower limb following an acute neurological event, given the resubmission claimed clinical non-inferiority to Botox® and based on the totality of evidence presented across the original submission (acute LLFS following an acute event) and this resubmission (acute LLFS following a stroke).

1.5 The basis of the requested listing was a cost-minimisation of Dysport® to the nominated comparator, Botox®. The resubmission presented an indirect comparison

between Dysport® 1500U and Botox® 300-400U in terms of the reduction of spasticity as measured by the Modified Ashworth Scale (MAS). MAS measures the level of resistance to passive movement, and evaluates a combination of soft tissue contracture and spastic dystonia, in addition to spasticity itself. Functional outcomes reported in the previous submission were not included in this resubmission.

Table 1: Key components of the clinical issue addressed by the resubmission

Component	Description
Population	Patients who have moderate to severe lower limb spasticity, defined as MAS ≥ *3,* following stroke. The patient population was extended in the PSCR to include patients who have moderate to severe lower limb spasticity, defined as MAS ≥ 3, following an acute neurological event.
Intervention	Dysport® (AbobotulinumtoxinA, Clostridium botulinum type A toxin-haemagglutinin complex). The dose should not exceed 1500U every 12 weeks into the lower limbs. If treatment is required for both upper and lower limbs, the total dose also must not exceed 1500U.
Comparator	Botox® (onabotulinumtoxin A). The dose should not exceed 400U in a single injection session. If treatment is required for both upper and lower limbs, the total dose also must not exceed 400U. This maximum dose was not reported in the approved Botox® Product Information (paragraph 4.3, Botox® PSD, November 2018)*.
Outcomes	Spasticity, as measured by the MAS. Specifically, mean change in MAS at Week 4 and proportion of MAS responders (≥ 1 reduction in MAS) at Week 4.
Clinical claim	In patients with moderate to severe focal spasticity of the lower limb following a stroke, Dysport® is non-inferior to Botox® at reducing muscle spasticity with a similar safety/tolerability profile.

MAS = Modified Ashworth Scale; PSCR = pre-Sub-Committee response; PSD = Public Summary Document
* The Botox® PI (p44) stated that in clinical trials, the doses did not exceed 360U divided among selected muscles at any treatment session.
Source: Table 1.2, p17 of the resubmission

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty (packs)	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
CLOSTRIDIUM BOTULINUM TYPE A TOXIN-HAEMAGGLUTININ COMPLEX, 300 UNITS INJECTION, 1 VIAL	5	0	$[redacted]*	Dysport® Ipsen Pty Ltd
CLOSTRIDIUM BOTULINUM TYPE A TOXIN-HAEMAGGLUTININ COMPLEX, 500 UNITS INJECTION, 1 VIAL	3	0	$[redacted]*	Dysport® Ipsen Pty Ltd

Category/Program:	Section 100 (Botulinum Toxin Program)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity	Moderate to severe spasticity
Condition	~~Lower limb spasticity following stroke~~ *Spasticity of the lower limb following an acute event*
PBS indication:	Moderate to severe spasticity of the lower limb following ~~stroke~~ *an acute event*
Treatment phase:	Initial and continuing
Restriction:	☒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. 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 of 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.*
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 Standard management includes physiotherapy and/or oral spasticity agents.
Prescriber 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 Arrangement 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.*
Cautions:	Contraindications to treatment include known sensitivity to botulinum toxin

* DPMQ based on published price of Botox®
Source: Table 1.4.2.1, pp34-35 of the resubmission.

2.1 The sponsor again requested PBS listing for Dysport® 300U or 500U vials, with a maximum quantity to provide the maximum recommended dose of 1500U per treatment session and no repeats (treatment sessions are no sooner than every 12 weeks).

2.2 The requested price for 1500U of Dysport® (dispensed price for maximum quantity, DPMQ) increased to $[redacted] for 300U vials (approved ex-manufacturer price (AEMP) per 300U vial = $[redacted]) and $[redacted] for 500U vials (AEMP per 500U vial = $[redacted]), from $[redacted] for 300U vials (AEMP per 300U vial = $[redacted]) and $[redacted] for 500U vials (AEMP per 500U vial = $[redacted]) in the previous submission. The increase in price was based on assumed dose relativities, which were not supported by the evidence. The resubmission stated that the requested price was a "placeholder price" because the recommended price of Botox® for LLFS was unknown.

2.3 The requested AEMPs for Dysport® 300U and 500U vials presented in the resubmission were not consistent with the requested price presented in the PB11 form, which were based on the current AEMPs (per vial) for upper limb spasticity and were unchanged from the previous submission.

2.4 The resubmission presented a revised requested restriction for Dysport® 300U and 500U vials, based on the suggested changes by the PBAC. The amendments included the following:

- The eligible population only included patients with moderate to severe spasticity of the lower limbs following "stroke", instead of following "an acute event" in the previous submission.

- The restriction did not include the criteria requiring treatment to commence between 3 months and 2 years following the acute event. However, the financial estimates presented in the resubmission assumed patients only initiate treatment within the first 2 years following stroke.
- The restriction defined moderate to severe spasticity as MAS ≥ 3 at baseline, instead of MAS ≥ 2 in the previous submission.
- The restriction defined the continuation criteria as a reduction in MAS of at least 1 after two treatment periods, compared to an improvement in walking speed of at least 0.13 m/s after four treatment cycles in the previous submission.

2.5 The revised restriction excluded patients with spasticity due to other aetiologies (e.g. traumatic brain injury, infection, hypoxia) because the PBAC had previously noted there was limited data and, accordingly, a high-level of uncertainty surrounding the effect of BoNT for the treatment of spasticity resulting from events other than stroke (paragraph 7.3, Dysport® PSD, November 2018). However, the PBAC recommended Botox® for LLFS following "an acute neurological event" as requested by RMSANZ. The PBAC considered that despite the lack of clinical trials in these populations, the request was reasonable and biologically plausible (web outcome, Botox®, March 2019). As noted above, the PSCR requested to broaden the proposed PBS population to include patients with lower limb spasticity following an acute neurological event.

2.6 The proposed restriction did not limit use of Dysport® to four treatment cycles in the first year and two treatment cycles from the second year onwards. The PBAC noted expert opinion which indicated that re-injection intervals tended to increase with continued treatment and considered that a limit of four treatment periods per lower limb in the first year and two treatment periods per lower limb per year from Year 2 onwards might be reasonable" (paragraph 2.4 and 7.13, Dysport® PSD, November 2018).

2.7 The PBAC noted that the resubmission accepted the majority of the comments and suggestions relating to the proposed restriction made during the evaluation of the November 2018 submission.

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

3 Background

Registration status

3.1 Dysport® was TGA registered on 16 March 2018 for "symptomatic treatment of focal spasticity affecting the lower limbs in adults". Other approved indications include focal spasticity of the lower limbs in children, focal spasticity of the upper limbs, spasmodic torticollis, blepharospasm, hemifacial spasm and glabellar lines. The approved indications were unchanged from the previous submission.

Previous PBAC considerations

3.2 In November 2018, the PBAC considered two major submissions (Dysport® and Botox®) to list BoNT for treatment of moderate to severe spasticity of the lower limb following stroke or an acute event. The PBAC did not recommend Dysport® (see below) and deferred the decision for Botox®. In March 2019, the PBAC considered a minor submission for Botox® and recommended listing for the treatment of LLFS following "an acute neurological event".

3.3 The PBAC did not recommend the PBS listing of Dysport® on the basis of uncertain clinical effectiveness, a high and uncertain incremental cost-effectiveness ratio (ICER) which was based on a flawed economic evaluation and uncertain financial estimates (paragraph 7.1, Dysport® PSD, November 2018). The previous submission modelled an improvement in walking speed and corresponding improvement in quality of life; however, the clinical evidence did not demonstrate any improvement in walking speed nor quality of life.

3.4 The resubmission did not address concerns regarding uncertain clinical effectiveness or cost-effectiveness given no new data was available and the resubmission did not present a modelled economic evaluation. The PBAC acknowledged that uncertainty surrounding the treatment effect was unlikely to be reduced by future high quality data and such data were not likely to become available (paragraph 7.12, Dysport® PSD, November 2018).

3.5 In May 2019, the MSAC Executive considered that MBS item 18360 was appropriate to administer BoNT to patients with lower limb spasticity.

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

4 Population and disease

4.1 Spasticity of the lower limb (adults) typically affects the hip, knee, ankle and foot. Focal spasticity affects a concentrated muscle area; examples in the lower limb include the equinovarus foot, valgus foot, striatal toe, stiff knee, flexed knee, adducted thighs, and flexed hip. These deformities may impede bed positioning, sitting balance, chair-level activities, transfers and standing up which limits mobility, pain and contractures, and impact on activities of daily living.

4.2 Dysport® is a muscle relaxant that acts on the junctions between the nerves and muscles, preventing the release of one of the chemical messengers called acetylcholine from the nerve endings that would normally cause the muscle to contract. This results in a weakened muscle and helps to reduce some of the abnormal muscle contractions.

4.3 Local and international guidelines recommend treatment with BoNT as adjuvant therapy to physical therapy (including postural management, physiotherapy, splints) and/or muscle blocking drugs. The proposed PBS listing for Dysport® is for use as an

adjunct to physical therapy, or as second line therapy when standard management has failed. Standard management includes physiotherapy and/or oral spasticity agents.

4.4 Dysport® is administered by intramuscular injection with the dose divided between affected muscles depending on the size, number and location of muscles involved, how severe the spasticity is, and taking into account any local muscle weakness and previous response to treatment. Injections are given approximately every 12 to 16 weeks, or as required to maintain the response but no more frequently than every 12 weeks.

4.5 The maximum dose must not exceed 1500U in the lower limbs. If treatment is required for both upper and lower limbs, the total dose also must not exceed 1500U. The resubmission relied on the clinical evidence for patients treated with Dysport® 1500U only from Study 140. Patients treated with the lower 1000U dose did not demonstrate a benefit.

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

5 Comparator

5.1 The resubmission nominated Botox® as the main comparator. The ESC considered that Botox® was the appropriate comparator.

5.2 One unit of Dysport® is not equivalent to one unit of Botox®. The maximum dose of Botox® in the lower limbs is 400U, given no more frequently than every 12 weeks. If treatment is required for both upper and lower limbs, the total dose also must not exceed 400U.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item. However, the PBAC noted that the consumer comments from the November 2018 submission were supportive of the listing, and outlined a range of benefits of treatment with Dysport® including improved mobility, improved quality of life, reduced pain and a reduced burden of care for carers and family.

Clinical trials

6.3 The resubmission presented an indirect comparison of Dysport® versus Botox® using placebo as common reference. The clinical evidence included data from three single-

dose double blind randomised controlled trials, comparing Dysport® 1500U (Study 140), Botox® 300U (Trial 512) or Botox® 300U to 400U (REFLEX) to placebo.

6.4 Details of the trials presented in the resubmission are provided in Table 2.

Table 2: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
Study 140	Clinical study report (CSR) - A Phase III, Multicentre, Double Blind, Prospective, Randomised, Placebo Controlled Trial, Assessing the Efficacy and Safety of Dysport® Used for the treatment of lower limb spasticity in adult subjects with hemiparesis due to stroke or traumatic brain injury.	CSR Study 140, 2015
Study 142 (extension study)	Clinical study report (CSR) – A Phase III, Multicentre, Open Label, Extension Trial to Assess the Long Term Safety and Efficacy of Repeated Treatment of Dysport® Intramuscular Injection in the Treatment of Lower Limb Spasticity in Adult Subjects with Spastic Hemiparesis Due to Stroke or Traumatic Brain Injury.	CSR Study 142, 2016
	Gracies JM, Esquenazi A, Brashear A, et al. Efficacy and safety of abobotulinumtoxinA in spastic lower limb, Randomised trial and extension.	Neurology, 2017; 86:2245-2253
REFLEX	Wein T, Esquenazi A, Jost WH, et al. OnabotulinumtoxinA for the treatment of post-stroke distal lower-limb spasticity: a randomized trial.	PM R. 2018 Jul 10(7):693-703.
Trial 512	Kaji R, Osako Y, Suyama K, et al. 2010. Botulinum toxin type A in post-stroke lower limb spasticity: a multicenter, double-blind, placebo-controlled trial.	J Neurol. 257(8): 1330-1337.

Source: Table 2.5, p.43 of the resubmission; Botox® publications

6.5 The PBAC had previously considered the clinical evidence from the three included trials in the November 2018 submissions of Dysport® and Botox®. No new trials were identified. Based on these trials, the resubmission presented an indirect comparison for the improvement in MAS from baseline to Week 4.

6.6 The resubmission excluded all other trials of Dysport® and Botox® presented in the November 2018 submissions. The updated literature search and exclusion of trials was poorly described and justified. The resubmission excluded trials that did not measure MAS, but MAS is only one of several important outcomes. In addition, the resubmission excluded two trials (Study 044 and Study 700) that reported MAS and compared the Dysport® 1500U to placebo in the relevant population (i.e. LLFS following stroke) without adequate justification. The PSCR stated that Study 044 and Study 700 were presented in detail as an appendix to the original submission in November 2018 and were determined by the evaluation then to be "less applicable to the proposed listing than the main trial (Study 140) due to differences in reported outcomes, data analysis and/or administration of lower doses of Dysport®".

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

Table 3: Key features of the included evidence

Trial	N	Population	Design/ duration	Interventions	Key Outcomes	Bias
Dysport® vs. PBO						
Study 140 [Multi-country]	ITT: 388 *PBS: 249*	ITT: Spastic hemiparesis causing gait dysfunction post-stroke or TBI (≥ 6 months prior), GSC MAS ≥ 2 in toxin-naïve or MAS ≥ 3 in toxin-experienced PBS population: Subgroup post-stroke with MAS ≥ 3	P3, R, DB; 12-24 week follow-up	**Interventions:** - DB phase: single injection Dysport® (1000U or 1500U) vs. PBO. - OL phase: four injections every 12-24 weeks Dysport® 1500U (or 1000U if AEs). **Muscles injected** (ES-guided): - Mandatory: Gastrocnemius, soleus - Optional: ≥ 1 other LL muscle[a] **Concomitant physical therapy:** - DB phase physiotherapy: Dysport® 1500U: 58.5%; PBO: 60.2%.	Primary: ΔMAS GSC at week 4 Other: ΔMAS GSC ≥ 1 at week 4	Low
Study 142 (140 OL-extension)	345		OL; 6-18 month follow-up		Long term safety and efficacy	High
Botox® vs. PBO						
REFLEX (Wein 2018) [Multi-country]	468	ITT: Spastic equinus or equinovarus post-stroke (≥ 3 months prior), ankle MAS ≥ 3.	DB phase: P3, R; 12 week follow-up OL phase: 60 week follow-up	**Interventions:** - DB phase: single injection Botox® 400U (300U mandatory + ≤ 100U optional muscles) vs PBO - OL phase: three injections Botox® 400U every ≥ 12 weeks **Muscles injection** (EMG/ES-guided): - Mandatory: Ankle plantar flexors − Gastrocnemius (medial and lateral), soleus, and tibialis posterior - Optional: ≥ 1 other LL muscle[b] **Concomitant physical therapy:** - DB phase physiotherapy: NR	Primary: ΔMAS-B (ankle plantar flexors) at average of weeks 4/6 Other: ΔMAS-B (ankle plantar flexors) at week 4 ΔMAS-B (ankle plantar flexors) ≥ 1 reduction at week 4	Low
Trial 512 (Kaji 2010) [Japan]	120	ITT: Spastic equinus post-stroke (≥ 6 months prior), ankle MAS ≥ 3	DB phase: P3, R; 12 week follow-up OL phase: 48 week follow-up, results NR	**Interventions:** - DB phase: single injection Botox® 300U vs PBO **Muscles injection** (EMG-guided): - Mandatory: Ankle plantar flexors − Gastrocnemius (medial and lateral), soleus, tibialis posterior **Concomitant physical therapy:** - DB phase: any rehabilitation in 58.6% Botox, 53.2% PBO	Primary: ΔMAS (ankle) AUC at week 12 Secondary: ΔMAS (ankle plantar flexors) at week 4	Low

AE = adverse event; AUC = area under the curve; DB = double blind; EMG = electromyography; ES = electrical stimulation; GSC = gastrocnemius soleus complex; ITT = intention to treat; LL = lower limb; MAS = Modified Ashworth Scale; MAS-B = Modified Ashworth Scale – Bohannon; NR = not reported; OL = open label; PBS = Pharmaceutical Benefits Scheme; PBO = placebo; P2 = Phase 2; P3 = Phase 3; P4 = Phase 4; R = randomised; TBI = traumatic brain injury

[a] Toe flexors, rectus femoris, hamstrings, other hip muscles. Tibialis posterior was injected in 73% of patients.

[b] Toe flexors, rectus femoris, hamstrings.

Source: Table 2.9-2.11, pp49-52 of the resubmission; Gracies 2017; Botox® PSD November 2018

6.8 The resubmission presented results for a post-hoc subgroup in Study 140 with LLFS following stroke and MAS ≥ 3 (which included 64% of the trial participants), to align with the requested restriction. Baseline characteristics and muscles and doses injected were provided in the PSCR. All patients enrolled in the Botox® trials met the PBS criteria. All of the trials enrolled patients with LLFS related to the foot/ankle

(gastrocnemius soleus complex, GSC), whereas the requested restriction permits treatment of other lower limb areas including toes, knees, thighs and hips. The PBAC recalled that it had previously considered that based on biological plausibility, the effect of Dysport® could be extrapolated to other muscle groups (paragraph 7.3, Dysport® PSD, November 2018).

6.9 Study 140 randomised patients to two doses of Dysport® (1000U or 1500U). The resubmission only presented an indirect comparison between Dysport® 1500U and Botox® because the PBAC had previously considered that Dysport® 1000U was not superior to placebo in terms of effectiveness (paragraph 6.33, Dysport® PSD, November 2018).

6.10 The Botox® trials and PBS subgroup of Study 140 assessed the efficacy at Week 4 after a single-dose of BoNT (Dysport® or Botox®) versus placebo for the treatment of LLFS in adults after stroke. The ESC considered that there were a number of important differences across the trials that might have biased the meta-analysis of the Botox® trials and limited the exchangeability of the three trials in the indirect comparison:

- Study 140 and REFLEX were multi-centre multi-country trials, whereas Trial 512 only enrolled Japanese patients.
- Across the trials, there were limited data about concomitant medications. Muscle relaxants and oral anti-spasticity agents were permitted in Study 140 (if initiated ≥ 4 weeks previously) and REFLEX (on a stable dose ≥ 2 months before day 1), whereas the use peripheral muscle relaxants was an exclusion criterion in Trial 512.
- The RMSANZ and international guidelines recommend BoNT treatment alongside physical therapy. However, the proportion of patients receiving concomitant physical therapy/physiotherapy in the trials was low (< 60%), and physiotherapy use was not reported in the REFLEX trial publication (Wein 2018).
- Beside differences in aetiology and baseline MAS (see above), the inclusion criteria also differed in terms of the location of spasticity. Study 140 enrolled patients with any hemiparesis with gait dysfunction (including hyperextended toe, equinovarus foot, flexed or extended knee and flexed hip), whereas the Botox® trials only included patients with equinus or equinovarus foot deformity.
- There were differences in important baseline characteristics across the trials. Approximately half of the patients in the PBS subgroup of Study 140 were BoNT-naïve, compared to all patients in Trial 512. Baseline MAS was also higher in the PBS subgroup of Study 140 (4.0 to 4.1) compared to the Botox® trials (3.1 to 3.3).
- There were also imbalances in prior BoNT treatment between the active and control arms of the post-hoc PBS subgroup in Study 140; approximately 47% of patients treated with Dysport® 1500U were BoNT-naïve compared to 54% treated with placebo.

- There were differences in the mandatory muscles injected across the trials, likely due to the slightly different populations enrolled. In the Botox® trials, mandatory muscles included the gastrocnemius (medial and lateral heads), soleus and tibialis posterior, which are key target muscles for equinus or equinovarus foot deformity. In Study 140, which enrolled patients with spasticity at other locations, mandatory muscles included the gastrocnemius (medial or lateral heads), soleus, and at least one additional muscle injected at the physician's discretion.
- All trials measured the improvement in MAS at the ankle flexor muscles at Week 4; however, there were differences in the coding of MAS during the analysis across the trials. Study 140 and REFLEX used the 'derived' coding system whereas Trial 512 used the 'historical' code. These differences affected the exchangeability of estimates for the mean change in MAS from baseline.

Comparative effectiveness

6.11 The resubmission presented an indirect comparison between Dysport® 1500U and Botox® 300-400U for the outcomes of mean change in MAS from baseline and proportion of responders (reduction in MAS ≥ 1) at Week 4. The PBAC noted that due to the limited exchangeability between Dysport® and Botox® trials, week 4 was the only common time point.

6.12 The resubmission also presented functional outcomes in Study 140 (e.g. physician global assessment, comfortable barefoot walking speed), which were unchanged from the original submission. The Botox® trials reported similar outcomes (e.g. clinical impression scale, goal assessment scale, gait analysis); however, the resubmission did not report these results or present any comparisons with Dysport®.

6.13 The ESC recalled that the PBAC had previously considered that MAS changes should be supported by functional improvements. In considering Botox® for LLFS, the PBAC "considered that an improvement of at least 1 MAS point, when accompanied with other functional improvements, was reflective of the trial-defined response outcome and likely to reflect a patient relevant response in some patients" (paragraph 2.4, Botox® PSD, November 2018). However, in considering Dysport® for LLFS, the PBAC "considered that a change in MAS of at least two using the 'derived MAS' convention, when accompanied by other functional outcomes such as goal attainment, would likely represent a clinically meaningful response.

6.14 Table 4 presents the results of the indirect comparison between Dysport® and Botox®. Results were updated during the evaluation to correct errors identified in the resubmission and include the proportion of MAS responders in Trial 512 (reported in the Botox® PSD, November 2018, and extracted during the evaluation).

6.15 The Statistical Analysis Plan for Study 140 and REFLEX specified adjustment of MAS change from baseline for differences in baseline covariates. The table below includes unadjusted results for the ITT population in Study 140, extracted from a STATA log file

during the evaluation. The resubmission only presented unadjusted results for the PBS subgroup in Study 140. Adjusted results for the PBS subgroup in Study 140 were presented in the PSCR.

Table 4: Indirect comparison Dysport® vs. Botox® - MAS change and responders

Trial ID	Dysport® 1500 U	Placebo	Botox® ≤ 400 U		
MAS mean change (SD) from baseline to Week 4				**Mean Difference (95% CI)**	
Study 140 (ITT unadj)	-0.7 (0.9)	-0.5 (0.7)		-0.2 (-0.41, 0.01)	
Study 140 (ITT adj)	-0.7 (0.9)	-0.5 (0.8)		**-0.3 (-0.5, -0.1)**	
Study 140 (PBS unadj)	-0.8 (1.0)	-0.5 (0.7)		**-0.29 (-0.56, -0.02)**	
Study 140 (PBS adj)	-0.81 (1.0)	-0.51 (0.7)		**-0.30 (-0.57, -0.03)**	
REFLEX		-0.61 (0.86)	- 0.81 (0.93)	**-0.20 (-0.36, -0.04)**	
Trial 512		-0.43 (0.72)	-0.88 (0.69)	**-0.45 (-0.70, -0.20)**	
MA Botox® vs. PBO				**-0.27 (-0.41, -0.14)**	
Indirect comparison of Dysport® (ITT unadj) vs Botox® MA				0.07 (-0.14, 0.28)	
Indirect comparison of Dysport® (ITT adj) vs Botox® MA				-0.03 (-0.23, 0.17)	
Indirect comparison of Dysport® (PBS unadj) vs Botox® MA				-0.02 (-0.29, 0.25)	
MAS mean change (SD) from baseline to Week 12				**Mean Difference (95% CI)**	
Study 140 (ITT unadj)	-0.5 (0.9)	-0.4 (0.7)		-0.13 (-0.32, 0.06)	
Study 140 (ITT adj)	-0.5 (0.9)	-0.4 (0.6)		**-0.2 (-0.4, 0.0)**	
Study 140 (PBS unadj)	-0.7 (1.0)	-0.4 (0.7)		**-0.3 (-0.55, -0.04)**	
REFLEX		NR	NR	NR	
Trial 512		-0.40 (0.58)	−0.56 (0.69)	-0.16 (-0.39, 0.07)	
Indirect comparison of Dysport® (ITT adj) vs Botox® Trial 512				-0.04 (-0.24, 0.16)	
Indirect comparison of Dysport® (ITT unadj) vs Botox® Trial 512				0.03 (-0.16, 0.22)	
Indirect comparison of Dysport® (PBS unadj) vs Botox® Trial 512				-0.14 (-0.40, 0.12)	
MAS responder analysis at Week 4				**RR (95% CI)**	**RD (95% CI)**
Study 140 (ITT)	60/128 (46.8%)	47/128 (36.7%)		1.28 (0.95, 1.71)	0.10 (-0.02, 0.22)
Study 140 (PBS)	43/83 (51.8%)	34/87 (39.1%)		1.33 (0.95, 1.85)	0.13 (-0.02, 0.28)
REFLEX		89/229 (38.9%)	117/225 (52%)	**1.34 (1.09, 1.64)**	**0.13 (0.04, 0.22)**
Trial 512		19/62 (30.6%)	38/58 (65.5%)	**2.14 (1.41, 3.25)**	**0.35 (0.18, 0.52)**
MA Botox® vs. PBO				**1.48 (1.23, 1.77)**	**0.18 (0.10, 0.26)**
Indirect comparison of Dysport® (ITT) vs Botox® MA				0.86 (0.61, 1.22)	-0.08 (-0.20, 0.04)
Indirect comparison of Dysport® (PBS) vs Botox® MA				0.84 (0.57, 1.23)	-0.05 (-0.20, 0.10)

adj = adjusted; CI = confidence interval; ITT = intention to treat; MA = meta-analysis; MAS = Modified Ashworth Scale; NR = not reported; PBO = placebo; PBS = Pharmaceutical Benefit Scheme; RD = risk difference; RR = risk ratio; SD = standard deviation; unadj = unadjusted
Some figures were recalculated during the evaluation using the sponsor's log file and Botox PSD, using RevManager 5.3. There were some errors in Table 2.48, page 98 of the resubmission: Week 4 results in Trial 512 were used instead of Week 12 results affecting the indirect comparison at Week 12; the resubmission also reported the unadjusted results in the ITT analysis of the mean change from baseline to Week 12 instead of the adjusted analysis included in the CSR.
Source: Table 2.52, p100; Tables 2.47, 2.48, 2.49, 2.50, pp98-99 of the resubmission. Table 16, Table 19 of Study 140 CSR and Table 3, p6 of the PSCR

6.16 The results demonstrated:

- Dysport® 1500U significantly reduced mean MAS compared to placebo at Week 4 and 12 in the ITT population (adjusted for study centre, baseline MAS, prior BoNT) and PBS subgroup (unadjusted and adjusted at Week 4 only) of Study 140. There were no significant differences between Dysport® and placebo in the unadjusted ITT analysis at Week 4 and 12, but the differences became significant in the

adjusted analysis.

- Botox® 300-400U significantly reduced mean MAS compared to placebo at Week 4 in REFLEX (adjusted for study centre, baseline MAS, optional muscles injected) and Trial 512 (unadjusted).
- There were no significant differences between Dysport® 1500U and placebo in the proportion of MAS responders (reduction in MAS ≥ 1) at Week 4 for the ITT population and PBS subgroup.
- The proportion of responders at Week 4 was significantly higher for Botox® compared to placebo in REFLEX and Trial 512.
- There were no significant differences between Dysport® 1500U and Botox® 300-400U for the outcomes of mean change in MAS at Week 4 and 12, or proportion of MAS responders at Week 4.

6.17 The resubmission stated that the indirect comparison demonstrated non-inferiority between Dysport® and Botox® because the upper 95% confidence interval (CI) was lower than the nominated non-inferiority margin (MAS difference < 1). The selection of this non-inferiority margin and subsequent claim of non-inferiority was unclear and not adequately justified. The ESC noted that none of the trials demonstrated a clinically meaningful improvement in mean reduction in MAS (i.e. MCID ≥ 1) for BoNT versus placebo at Week 4 or 12.

6.18 The pre-PBAC response stated that Study 142, which presented the extension study of Dysport® and which was considered at the November 2018 PBAC meeting, demonstrated increased improvements with subsequent cycles of Dysport® 1500U (mean change in MAS of -1.0 (0.9) at Week 4 of Cycle 3). As noted previously, the evidence presented in Study 142 did not provide comparative efficacy data versus placebo, given all patients in the open label extension phase received active treatment, and the number of patients decreased over time, suggesting that those remaining in the study were responders (paragraph 6.18, Dysport® PSD, November 2018).

Comparative harms

6.19 Table 5 summarises an indirect comparison between Dysport® and Botox® for safety outcomes after 12 weeks of treatment (e.g. a single injection). The table does not

include results from REFLEX because the trial publication only reported safety outcomes pooled over the double blind and open label phases.

Table 5: Indirect comparison Dysport® vs. Botox® - Safety outcomes at Week 12

	BoNT (%)	Placebo (%)	RR (95% CI)	RD (95% CI)
Any AE				
Study 140, Dysport® 1500U	52/128 (40.6%)	41/130 (31.5%)	1.29 (0.93, 1.79)	0.09 (-0.03, 0.21)
Trial 512, Botox® 300U	26/58 (44.8%)	27/62 (43.5%)	1.03 (0.69, 1.54)	0.01 (-0.17, 0.19)
Indirect comparison Dysport® vs. Botox®			1.25 (0.75, 2.10)	0.08 (-0.04, 0.20)
TEAE				
Study 140, Dysport® 1500U	16/128 (12.5%)	8/130 (6.2%)	2.03 (0.90, 4.58)	0.06 (-0.01, 0.13)
Trial 512, Botox® 300U	7/58 (12.1%)	7/62 (11.3%)	1.07 (0.40, 2.86)	0.01 (-0.11, 0.12)
Indirect comparison Dysport® vs. Botox®			1.90 (0.53, 6.80)	0.05 (-0.02, 0.12)
SAE				
Study 140, Dysport® 1500U	5/128 (3.9%)	7/130 (5.4%)	0.73 (0.24, 2.23)	-0.01 (-0.07, 0.04)
Trial 512, Botox® 300U	5/58 (8.6%)	1/62 (1.6%)	5.34 (0.64, 44.39)	0.07 (-0.01, 0.15)
Indirect comparison Dysport® vs. Botox®			0.14 (0.01, 1.50)	**-0.08 (-0.14, -0.03)**

AE = adverse events; BoNT = botulinum toxin; CI = confidence interval; RD = risk difference; RR = risk ratio; SAE = serious adverse events; TEAE = treatment emergent adverse events

Indirect comparison figures were recalculated during the evaluation using the sponsor's log file and Botox® PSD November 2018, using RevManager 5.3

Source: Table 2.53, p101 of the resubmission.

6.20 The ESC considered that Dysport® and Botox® presented similar adverse event profiles. There were no significant differences between Dysport® and Botox® for any adverse events and treatment-emergent adverse events. There was a higher incidence of serious adverse events with Botox®; however, the number of serious adverse events in Trial 512 was low (5 in the Botox® arm and 1 in the placebo arm) and the study authors stated that all of the serious adverse events, with the exception of myalgia, were considered to be unrelated to Botox®.

Benefits/harms

6.21 Based on the non-inferiority results presented in the resubmission, and the indirect treatment comparison, no benefits and harms table was presented.

Clinical claim

6.22 Based on the results of an indirect comparison of change in MAS, the resubmission described Dysport® 1500U as non-inferior in terms of effectiveness and safety compared to Botox® 300-400U for the treatment of moderate to severe (MAS ≥ 3) LLFS following stroke.

6.23 The ESC considered that the claim of non-inferior safety was reasonable.

6.24 The ESC considered that the claim of non-inferior effectiveness of Dysport® 1500U versus Botox® 300-400U was likely to reasonable; however, required consideration, given that:

- across the included trials, there were differences in the location of spasticity of included patients, muscles treated, concomitant therapies, and how change in

MAS outcome was coded (historical vs derived coding systems) in the analysis;

- there were differences in important baseline characteristics across the trials and a large difference in prior BoNT treatment across arms in the post-hoc PBS subgroup of Study 140, which may have affected the outcomes;
- the PSCR did not provide adjusted results for the analysis of the PBS subgroup of Study 140 for baseline MAS, prior BoNT and study centre in-line with the statistical analysis plan for change in MAS to Week 12;
- the interpretation of the indirect comparison was unclear given that the selection of the non-inferiority margin was not adequately justified and none of the trials demonstrated a clinically meaningful improvement in mean reduction in MAS for BoNT versus placebo, and the confidence intervals of the indirect comparison included the point estimates versus placebo; and
- the doses nominated in the claim (i.e. 1500U of Dysport® non-inferior to 300-400U of Botox®) did not accurately reflect the amount of BoNT injected into key muscles across the trials. Based on a dose relativity of 3.75U Dysport® to 1U Botox® (see Economic analysis below), Dysport® 1500U should be compared to Botox® 400U (i.e. the maximum doses).

6.25 The PBAC had previously considered that the uncertainty surrounding the treatment effect of Dysport® for LLFS could be mitigated through adjustment of the requested price (paragraph 7.12, Dysport® PSD, November 2018). At the March 2019 meeting, the PBAC had considered that a Special Pricing Arrangement and Risk Share Arrangement helped mitigate the outstanding uncertainty surrounding the clinical benefit, cost-effectiveness and financial implications associated with extending the listing of Dysport® in the upper limb following stroke, to also include spasticity following acute events others than stroke (web outcome, Dysport®, March 2019).

6.26 The PBAC considered that the claim that Dysport® was non-inferior to Botox® in terms of comparative effectiveness was likely to be reasonable.

6.27 The PBAC considered that the claim that Dysport® was non-inferior to Botox® in terms of comparative safety was reasonable.

Economic analysis

6.28 The resubmission presented a cost minimisation analysis, comparing drug costs (no other costs or cost-offsets) of a single injection session with Dysport® 1500U and Botox® 400U. The analysis used the current list price of Botox® 400U for upper limb spasticity ($[redacted]) as a placeholder price given the sponsor was unaware of the recommended list price for lower limb spasticity.

6.29 The cost minimisation analysis assumed 2.66U of Dysport® was equi-effective to 1U of Botox®, based on the mean dose of Dysport® injected into the GSC (reported as

796.9U) in Study 140 and the maximum dose of Botox® injected into the GSC plus tibialis posterior (300U) in the Botox® trials.

6.30 The resulting estimated cost per cycle (i.e. the maximum AEMP) for treatment with Dysport® 1500U ($[redacted]) was significantly more costly than treatment with Botox® 400U ($[redacted]). However, the ESC considered that the nominated equi-effective doses were not appropriate for the following reasons:

- The maximum dose of Botox® injected into the GSC was 225U, not 300U as assumed.
- The resubmission proposed that only the dose injected into the GSC was relevant when comparing MAS measured at the GSC. This rationale was poorly justified. The CSR for Study 142 (the OL phase of Study 140) stated that Dysport® injections to the flexor longus muscles and the tibialis posterior muscle also had an impact on the MAS of the ankle joint, in view of their action on plantarflexion of the ankle.
- The resubmission did not report the mean doses and/or muscles injected for patients in the PBS subgroup of Study 140.
- The comparison of a mean dose to a maximum dose was not reasonable given they may not be equivalent. The trial publications did not report the mean doses of Botox® administered; hence, it would have been more reasonable to compare maximum doses of Dysport® and Botox®.
- The cost minimised prices for Dysport® and Botox® should include similar wastage. The ESC noted that BoNT must be refrigerated and that vials are single use only. Therefore, the ESC considered that in practice, clinicians would prescribe either 1500U of Dysport® or 400U of Botox®, even if the doses administered were slightly lower.

6.31 Table 6 summarises the doses injected by muscle group in Study 140 and the Botox® trials, and the corresponding equi-effective doses.

Table 6: Mean/Maximum doses injected and equi-effective dose estimation^

	Dysport® 1500U Mean dose	**Botox® 300-400U Maximum dose**	**Dysport® equi-effective dose to Botox® 1U**
CMA – GSC only	796.9U	300U	2.66U
GSC only	796.9U	225U	3.54U
All sites	1488.4U	400U*	3.72U
GSC + Tibialis posterior	1108.5U PSCR: 995.5U	300U	3.69U PSCR: 3.31U
Maximum dose	1500U	400U	3.75U

CMA = cost-minimisation analysis; GSC = gastrocnemius-soleus complex; PSCR = pre-Sub-Committee response

^ Patients in Dysport® had MAS≥2 while in the Botox® Trials baseline MAS≥3

* Patients in REFLEX received Botox® 300U into the muscles contributing to the primary outcome measure, with a further 100U permitted to be used elsewhere in the lower limbs.

Source: Table 3.2 (p107), Tables 2.25-2.26 (pp69-70) of the resubmission, pp2-3 of the PSCR

6.32 The PSCR considered that it was an error to sum the average doses of Dysport® by muscle in the GSC without taking into consideration the proportion of patients who received an injection into that muscle. Using a weighted dose per muscle group resulted in an equi-effective dose, which was proposed as an alternate equi-effective dose in the PSCR, of 3.3U Dysport® to 1U Botox®.

6.33 The PSCR considered that the use of the maximum dispensed quantities (i.e. 1500U Dysport® and 400U Botox®) were not appropriate to inform the calculation of equi-effective doses (3.75U Dysport® to 1U Botox®) as neither of these doses directly contributed to the therapeutic outcomes.

6.34 Overall, the ESC considered that in practice patients will be prescribed the maximum quantity of Dysport® (1500U) or Botox® (400U). The ESC considered that the use of any equi-effective dose other than that those based on the maximum dispensed quantities would not result in equivalent treatment costs per cycle and therefore, would not be appropriate. The ESC advised that the cost per cycle of Dysport® must equal the cost per cycle of Botox® and that the equi-effective doses were:

3.75U Dysport® = 1U Botox®

6.35 The pre-PBAC response reiterated that the equi-effective doses should be based on the mean therapeutic dose that produces the clinical outcomes observed in the clinical evidence, and that the equi-effective doses were 3.3U Dysport® to 1U Botox® (i.e. 995.5U Dysport® and 300U Botox®). The pre-PBAC response noted that, incorporating wastage, this was equivalent to two vials of 500U Dysport® and three vials of 100U Botox®.

Drug cost/patient/cycle

6.36 The drug cost per patient was $[redacted] per treatment cycle (i.e. DPMQ for 1500U). The estimate did not include costs for administration (MBS item 18360) or follow-up visits to monitor response (MBS item 116).

6.37 In the financial estimates, the resubmission assumed all patients that met the continuation criteria after two cycles received 3.72 treatment cycles per year indefinitely, which was a likely overestimate. Data considered previously by the PBAC indicated reinjection intervals tended to increase over time (see paragraph 2.6 above).

Estimated PBS usage & financial implications

6.38 The resubmission was not considered by DUSC. As with the previous submission, the resubmission used an epidemiological approach to estimate the financial impact of listing Dysport® on the PBS.

6.39 The methodology was largely unchanged from the November 2018 submission; however, the resubmission updated several of the key parameters in the financial model. Overall, the net effect of the parameter changes increased the number of patients in the eligible population with LLFS post-stroke, and considerably increased the total number of patients treated over time. The resubmission assumed no patients

discontinued treatment and all patients received 3.72 cycles per year, which was considered unreasonable.

6.40 The updated financial estimates did not include any grandfathering of patients currently treated with BoNT and excluded patients with LLFS from initiating treatment with BoNT if the stroke occurred more than 2 years prior to Year 1. This assumption may not be reasonable given such patients would now be eligible for treatment under the requested restriction presented in the resubmission.

6.41 Table 7 summarises the estimated use and financial implications for the proposed Dysport® PBS listing. The table below shows the financial estimates with the DPMQ requested in the resubmission ($[redacted]).

6.42 The PSCR provided updated financial estimates based on the request to extend the proposed PBS listing to include patients with lower limb spasticity following an acute neurological event and the updated equi-effective dose (3.3U Dysport® to 1U of Botox®).

Table 7: Estimated use and financial implications

		Year 1 (2020)	Year 2 (2021)	Year 3 (2022)	Year 4 (2023)	Year 5 (2024)	Year 6 (2025)
A	Australian aged 18+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B	Eligible incident patients#	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C	Eligible prevalent patients*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
D	**Total eligible patients (B+C)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
E	Treatment cycles per year^	3.72	3.72	3.72	3.72	3.72	3.72
F	Total services per year (DxE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dysport® 300U (17.6%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dysport® 500U (82.4%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
G	PBS/RPBS cost‡	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
H	Patient co-payment	($[redacted])	($[redacted])	($[redacted])	($[redacted])	($[redacted])	($[redacted])
I	**Net cost to PBS/RPBS**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**
J	Net cost to MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
K	Net cost to health budget	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
PSCR - Updated patient numbers and financial implications (all acute neurological events)							
Incident patients treated		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prevalent patients treated		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total treated patients		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dysport® 300U injections		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dysport® 500U injections		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to PBS/RPBS		**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**
Net cost to heath budget		$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
November 2018 submission (all acute neurological events)							
		Year 1 (2019)	**Year 2 (2020)**	**Year 3 (2021)**	**Year 4 (2022)**	**Year 5 (2023)**	**Year 6 (2024)**
Total patients treated		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other aeteologies		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Dysport® services		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other aeteologies		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to PBS/RPBS		**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**
Stroke		$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Other aeteologies		$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cos to health budget		$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Stroke		$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Other aeteologies		$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

LL = lower limb; DPMQ = dispensed price for maximum quantity; MAS = Modified Ashworth Scale; MBS = Medical Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

Incident patients = Australian aged 18+ x (incidence rate) x (proportion resulting in spasticity) x (proportion with LL spasticity x proportion with MAS ≥ 3) x (proportion failing first line therapy or use Dysport® as adjunct to physical therapy) x (proportion of eligible patients receiving treatment)

* Prevalent patients comprised of incident patients from prior years (whose event was ≤ 2 years) x annual mortality (Year 1: 26%, Year 2 to Year 6: 5.50%)

[a] Incident population in 2019 estimated as [redacted], i.e. [redacted] = [redacted] * (1 - 0.26)

^ Based on the rate of retreatment (3.855114/378.8352) over 365.25 days

‡ Correcting the Section 4 Workbook for the resubmission's requested price (DPMQ for 300U is $[redacted] and 500U is $[redacted])

Source: Constructed during the evaluation from Section 4 of the resubmission and Section 4 Workbook.xlsx

The redacted table shows that at Year 6, the estimated number of patients was 10,000 – 50,000 per year and the net cost to the PBS would be $20 – $30 million per year.

6.43 The financial estimates were most sensitive to the size of the treated population (incidence and uptake) as well as the assumptions around continuation and number of treatment cycles in subsequent years. Whether the financial estimates were an under- or over-estimate was unclear, given the resubmission excluded a potentially large pool of prevalent patients but assumed those treated remained on treatment indefinitely.

6.44 Although the submission presented a cost minimisation analysis for Dysport® compared to Botox®, the ESC noted that the financial implications were high as Botox® is not currently listed on the PBS; therefore, the resubmission did not include cost offsets. The PSCR noted that given Dysport® is seeking a listing via a cost-minimisation analysis, the financial implications will ultimately be neutral. The ESC, noting that the proposed equi-effective dose in the PSCR was 3.3U Dysport® to 1U Botox®, considered that the listing of Dysport® could only be cost neutral to Botox® if the cost of the maximum dispensed quantity for both drugs was equivalent (i.e. 1500U of Dysport® and 400U of Botox®).

Quality Use of Medicines

6.45 No quality use of medicines information was presented in the resubmission and the resubmission did not include any proposals for post-marketing surveillance studies.

6.46 The PBAC agreed with ESC, noting that the dose calculation of Dysport® can be complicated if patients require administration in both the upper and lower limbs. In addition, Dysport® and Botox® are not interchangeable.

Financial Management – Risk Sharing Arrangements

6.47 The resubmission stated the sponsor was willing to enter a risk sharing arrangement (RSA) due to uncertainty in the estimated eligible population and the risk of leakage of Dysport® use outside of the requested restriction into non-stroke patients. The sponsor was willing to discuss the design of the RSA through the course of the resubmission, noting that an RSA was designed in March 2019 PBAC meeting whereby in their first year incident patients receive four Government-funded treatments, and in the remaining years, the Government would fund two injections while the sponsor rebates the cost of the remaining two.

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

7 PBAC Outcome

7.1 The PBAC recommended the Section 100 (Botulinum Toxin Program), Authority Required (STREAMLINED) listing of botulinum toxin type A (Dysport®) for focal spasticity of the lower limb (LLFS) following stroke or other acute neurological event on a cost minimisation basis with botulinum toxin type A (Botox®). On the basis of the indirect comparison presented, the PBAC was satisfied that Dysport® was non-inferior

to Botox® in terms of comparative efficacy and safety, and provided, for some patients, an improvement in efficacy over standard of care.

7.2 The PBAC recalled that the listing of botulinum toxin type A (BoNT) for the treatment of moderate to severe LLFS following stroke or other acute events (including traumatic brain and spinal cord injuries) was supported by the Rehabilitation Medicine Society of Australia and New Zealand (RMSANZ). The PBAC noted that it had previously considered that, despite the lack of clinical trials in patients with spasticity following an acute event other than stroke, that the effectiveness of BoNT in these patients was biologically plausible.

7.3 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. The PBAC considered that the equi-effective doses were:

3.75U Dysport® and 1U Botox® (i.e. 1500U Dysport® = 400U Botox®).

7.4 The PBAC considered that Botox® was the appropriate comparator.

7.5 The PBAC noted that the basis of the resubmission was an indirect comparison between Dysport® and Botox®, with placebo as the common reference. The key trials were three single dose, double blind, randomised controlled trials, comparing Dysport® 1500U (Study 140), Botox® 300U (Trial 512) and Botox® 300U to 400U (REFLEX) to placebo. The PBAC noted that it had considered Study 140 in relation to the November 2018 Dysport® submission and Trial 512 and REFLEX in the November 2018 and March 2019 Botox® submissions.

7.6 The PBAC noted that there were a number of important differences across the trials that might have biased the meta-analysis of the Botox® trials and limited the exchangeability of the three trials in the indirect comparison, including:

- Study 140 and REFLEX were multi-centre multi-country trials, whereas Trial 512 only enrolled Japanese patients;
- the inclusion criteria differed in terms of the location of spasticity, concomitant medications and prior BoNT treatment;
- differences in the baseline characteristics (including aetiology and baseline MAS score); and
- differences in the mandatory muscles injected and the coding of the Modified Ashworth Scale (MAS) during the analysis across the trials.

7.7 The PBAC noted that none of the key trials in the resubmission demonstrated a clinically meaningful improvement in mean reduction in MAS score (i.e. minimal clinical important difference ≥ 1) for botulinum toxin (BoNT) compared to placebo at Week 4 or, when reported, Week 12. However, the PBAC noted that the mean changes in MAS score at Week 4 in the PBS subgroups (adjusted and unadjusted) of the key Dysport® trial, Study 140, were statistically significant compared to placebo. The PBAC

considered that the magnitude of the benefit was small following the first cycle and, although comparative data were unavailable beyond the first cycle, noted that continued responses were observed in those who chose to continue with subsequent treatments in Study 142.

7.8 The PBAC considered that the uncertainty surrounding changes in MAS score after the first cycle and the incremental benefit of Dysport® could be mitigated by aligning its restriction with the recommended Botox® restriction for the treatment of LLFS. In particular, the continuation criteria would ensure that only responding patients (i.e. those achieving the clinical relevant difference of at least a one point change in MAS following the second cycle) would receive more than two cycles of BoNT. The PBAC noted the uncertainty surrounding the magnitude of the treatment effect was unlikely to be reduced by future high quality data.

7.9 The indirect comparison demonstrated no significant differences between Dysport® 1500U and Botox® 300-400U for the outcomes of mean change in MAS at Week 4 or 12 or proportion of MAS responders at Week 4.

7.10 Based on the results of the indirect comparison, the PBAC considered that the clinical claim that Dysport® 1500U was non-inferior to Botox® 300-400U in terms of effectiveness was likely to be reasonable, noting the number of significant differences between the key trials.

7.11 Based on the results of the indirect comparison, the PBAC considered that the claim that Dysport® was non-inferior in terms of comparative safety to Botox® was reasonable.

7.12 The PBAC noted that the resubmission addressed the issues identified with the November 2018 economic analysis by presenting a cost minimisation analysis, comparing drug costs of a single injection session with Dysport® 1500U and Botox® 400U. The PBAC considered that this was appropriate.

7.13 The PBAC considered that the equi-effective doses nominated in the resubmission (2.66U of Dysport® to 1U of Botox®) were not appropriate for the following reasons:

- The doses were based on the mean dose of Dysport® injected into the gastrocnemius soleus complex (GSC) in Study 140 (796.9U) and the assumed maximum dose of Botox® injected into the GSC plus tibialis posterior in the Botox® trials (300U). However, the maximum dose of Botox® injected into the GSC was 225U, not 300U as assumed. In addition, the comparison of a mean dose to a maximum dose was not reasonable given they may not be equivalent.
- The cost minimised prices for Dysport® and Botox® should include similar wastage as BoNT must be refrigerated and vials are single use only.

7.14 The PBAC noted that the equi-effective doses were updated in the PSCR to 3.3U Dysport® and 1U Botox®, using a weighted mean dose from Study 140 for Dysport® injected into both the GSC and the tibialis posterior (995.5U) and the incorrectly

assumed maximum dose of Botox® (300U).

7.15 The PBAC considered that in practice, patients would be prescribed the maximum quantity of Dysport® (1500U) or Botox® (400U). Given the uncertainty and lack of precision in the clinical comparison, the PBAC considered that the use of any equi-effective dose other than that those based on the maximum dispensed quantities would not result in equivalent treatment costs per cycle and therefore, would not be appropriate. Hence, the PBAC considered that the equi-effective doses were 3.75U Dysport® to 1U Botox®.

7.16 The PBAC considered that the estimated financial impact of Dysport® was uncertain and should be adjusted to:

- include LLFS due to other aetiologies as per the PSCR;
- remove the assumption for continuous therapy for all patients;
- align the number of treatments with that recommended for Botox® (i.e. a maximum of four treatment periods per lower limb in the first year of treatment, and two treatment periods per lower limb each year thereafter); and
- utilise the appropriate equi-effective dose (i.e. 3.75U Dysport® to 1U Botox®).

7.17 Like Botox®, the PBAC considered that the extent to which the potential use of Dysport® in both the upper and lower limbs in the same patient would affect utilisation, cost effectiveness and the financial implications remained uncertain. The Committee was therefore of the view that any pricing arrangements for these indications should take these uncertainties into account by implementing a single price across these conditions.

7.18 The PBAC considered that the restriction for Dysport® should, as per the recommended Botox restriction of LLFS, include the clinical criteria that treatment must not exceed a maximum of four treatment periods per lower limb in the first year of treatment and two treatment periods per lower limb each year thereafter.

7.19 The PBAC considered that a grandfather restriction may be appropriate for patients already treated with Dysport® who meet response criteria, if requested by the sponsor.

7.20 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because the Dysport® formulation of BoNT is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over the Botox® 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.

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

7.22 The PBAC reaffirmed that Dysport® remained unsuitable for prescribing by nurse

practitioners.

7.23 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.

7.24 The PBAC has previously advised that Xeomin®, Botox® and Dysport® should be treated as interchangeable on an individual patient basis under Section 101(3BA) of the National Health Act 1953.

7.25 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 Amend existing/recommended listing as follows:

The Secretariat aligned the proposed restriction to the same restriction wording as the Botox® listing.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
CLOSTRIDIUM TYPE A TOXIN-HAEMAGGLUTININ COMPLEX				
300 units injection, 1 vial	5	0	Dysport®	Ipsen Pty Ltd
500 units injection, 1 vial	3	0		

Category/Program:	Section 100 – Botulinum Toxin Program
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐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
Treatment phase:	Initial and continuing
Restriction Level/Method:	☒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, 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 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.
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 Note:	The units used to express the potency of botulinum toxin preparations currently available for PBS subsidy are not equivalent. Special Pricing Arrangement 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.
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 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:	☒Streamlined
Clinical criteria:	Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to <DATE>, AND 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 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 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.
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.

9 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.

10 Sponsor's Comment

The sponsor had no comment.