6.03 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 submission requested an extension of the current Section 100 (Botulinum Toxin Program), Authority Required (Streamlined) listing for Clostridium botulinum type A toxin-haemagglutinin complex (herein known as Dysport®) for treatment of moderate to severe focal spasticity of the upper limb following a stroke, to include spasticity following an acute event. An acute event was defined by the submission as an event that leads to an upper motor neuron lesion resulting in spasticity such as stroke, traumatic brain injury (TBI), spinal cord injury, infection or hypoxia.

1.2 This submission also requested the removal of the current maximum of four treatment periods per upper limb per lifetime restriction for Dysport® in upper limb focal spasticity.

1.3 At the November 2018 meeting the PBAC also considered a submission for Dysport® in the treatment of lower limb spasticity following an acute event (Item 6.02) and botulinum toxin type-A (BOTOX®) for the treatment of lower limb spasticity following a stroke (Item 7.02).

1.4 The basis for the requested extension of listing was cost-effectiveness of Dysport® (via a cost per responder analysis) compared with placebo.

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

Component	Description
Population	Patients with moderate to severe focal spasticity of the upper limb following an acute event (that leads to an upper motor neuron lesion resulting in spasticity such as a stroke, TBI, infection or hypoxia)
Intervention	Clostridium botulinum type A toxin – haemagglutinin C complex (Dysport®)
Comparator	Placebo or best supportive care
Outcomes	A range of measures of spasticity including: • Change in spasticity: measured as change in MAS score in the PTMG between baseline and week 4. • Functional gains: measured using PGA of overall treatment response at week 4; and change in DAS score for the PTT between baseline and week 4.
Clinical claim	In patients with moderate to severe focal spasticity of the upper limb following an acute event, Dysport® is more effective than placebo at improving MAS, PGA and DAS.

Abbreviations: DAS=Disability Assessment Scale; MAS=modified Ashworth scale; PGA=Physician's Global Assessment; PTMG=primary targeted muscle group; PTT=principal target of treatment; TBI=traumatic brain injury.
Source: Table 1.1, p20 of the submission.

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

2 Requested listing

2.1 Suggested additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty. (units)	№. of Rpts	DPMQ	Proprietary Name and Manufacturer	
CLOSTRIDIUM BOTULINUM TYPE A TOXIN-HAEMAGGLUTININ COMPLEX					
300 units injection, 1 vial	4	0	$1,221.85 (published)	Dysport®	Ipsen Pty Ltd
500 units injection, 1 vial	2	0	$1,094.79 (published)	Dysport®	Ipsen Pty Ltd

Category / Program :	Section 100 – Botulinum Toxin Program
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity	*Moderate to severe*
Condition:	*Spasticity of the* ~~Adult~~ upper limb ~~moderate to severe spasticity~~ *following an acute event*
PBS Indication:	Moderate to severe spasticity of the upper limb *following an acute event*
Treatment phase:	~~Initial and continuing~~
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined
Clinical criteria:	The condition must be moderate to severe spasticity of the upper limb/s following an acute event, defined as a Modified Ashworth Scale rating of ~~2~~ 3 or more, **AND** ~~The treatment must not be initiated until three months post-event,~~ **AND** The treatment must only be used as second line therapy when standard management has failed; OR The treatment must only be used as an adjunct to physical therapy, **AND** The treatment must not continue if the patient does not respond (defined as not having had a decrease in spasticity rating greater than 1, using the Modified Ashworth Scale, in at least one joint) after two treatment periods *(with any botulinum toxin type A),* **AND** Patient must not have established severe contracture in the limb to be treated.
Population criteria	Patient must be aged 18 years or older.
Treatment criteria:	Must be treated by a neurologist; OR Must be treated by an orthopaedic surgeon; OR Must be treated by a rehabilitation specialist; OR Must be treated by a plastic surgeon; OR Must be treated by a geriatrician.
Prescribing instructions	*The date and nature of the event must be documented in the patient's medical records when treatment is initiated.* *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.*
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, TBI, infection or hypoxia.
Caution	*Contraindications to treatment include known sensitivity to botulinum toxin.*

^ estimated during the evaluation using PB11 prices and updated PBS mark ups from July 2018. The submission quoted DPMQ of $1,221.71 and $1,094.65 respectively for the 300 unit and 500 unit injection preparations. Based on the requested AEMP of $293.64 and

$523.75 per vial for 300 unit and 500 unit strengths preparations respectively, the DPMQs would be slightly higher at $1,221.85 and $1,094.79 based on PBS mark ups from 1 July 2018. These correspond to prices in the July 2018 PBS schedule.
Source: Table 1.7, p33 of the submission.

2.2 The Sponsor requested the same prices as currently listed for treatment of spasticity of the upper limbs following stroke (PBS mark ups from 1 July 2018).

2.3 Two inconsistencies were noted between the submission's requested restriction and the current PBS restriction for spasticity following stroke.

2.4 Firstly, the current PBS restriction requires patients to have baseline spasticity level as measured by the Modified Ashworth Scale (MAS) of 3 or more, whereas the requested restrictions specified that patients only need a MAS score of 2 or more to be eligible. The submission provided no justification for this proposed change in eligibility criteria, nor noted this difference compared to the current post-stroke PBS listing. The PBAC had previously considered in the September 2002 resubmission for Dysport® in upper limb focal spasticity post-stroke that any restriction should include a definition of "moderate to severe" spasticity in terms of MAS of 3 or 4. See Table 2 for a description of MAS scores. In the PSCR it was stated that the request to adjust the PBS listing criterion to a MAS score of 2 or more was to align with the clinical evidence presented in Trial 145. The trial recruited patients who were naïve to toxin with a MAS score ≥ 2 and patients who were toxin experienced with a MAS score ≥ 3. The ESC noted that this would expand the PBS eligibility criteria to less severe patients compared to those previously considered to benefit from treatment. The PBAC acknowledged that the key trial enrolled toxin-naïve patients with a MAS ≥2; however, considered that this alone did not justify such a significant change to the PBS restriction. The PBAC noted that the mean baseline MAS score for patients enrolled in Study was 3.9.

2.5 Secondly, the requested restriction did not clearly state that treatment should stop if patients do not respond after two treatment periods (total Botox®, Dysport® and Xeomin®) as is specified in the current post-stroke PBS listing. The PSCR clarified that the stopping rule criterion was erroneously removed from the proposed restriction. The stopping rule should ensure that patients who do not respond to treatment do not continue to receive Dysport®.

2.6 A key difference between the requested restriction in this submission and the current PBS restriction was the removal of the maximum limit of four-treatments per limb per lifetime criteria. To support this request, the submission used evidence from Study 148, the open label extension of Study 145. However, in Study 148, the rollover subjects from Study 145 received a maximum of four treatment cycles (including the first cycle in the double blind trial Study 145), and de novo subjects received a maximum of five treatment cycles. Only 32% (81/254) of patients starting Cycle 1 continued onto Cycle 4, and only 4% (11/254) continued onto Cycle 5. Hence, Study 145 and Study 148 did not provide strong evidence to support efficacy and safety of Dysport® treatments beyond four cycles. The PSCR stated that the removal of the four treatment limit was also supported by the substantial proportion of patients who enrolled in Study 145 who had received prior botulinum toxin treatment (55%). The

ESC noted that it was unclear how many treatments were previously received, when patients had received them, or if they were given for the same diagnosis of spasticity. The pre-PBAC Response claimed that the proposed continuation stopping rule would prevent patients who do not respond to treatment from receiving additional botulinum toxin.

2.7 The submission also submitted a letter by the Rehabilitation Medicine Society of Australia and New Zealand (RMSANZ) supporting the removal of this restriction and noted that DUSC had recently also reviewed the PBS utilisation of botulinum toxin. Both of these items were considered by the PBAC in July 2018. Overall, DUSC considered the cost implications of the removal of the four treatment periods limitation per upper limb per lifetime in post-stroke patients would have small to negligible impact on PBS as the majority of patients only receive one to two treatment cycles (Item 10.06, July 2018, DUSC advice to PBAC on botulinum toxin).

2.8 The PBAC agreed that the removal of a lifetime limit of four treatments was consistent with clinical practice for continuing responders. 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.

2.9 The proposed PBS restriction defined response as a decrease in MAS of greater than one, in at least one joint, after two treatment periods. This was consistent with the current continuation criteria for Dysport® in upper limb focal spasticity. However, it is inconsistent with the submission's nominated minimal clinically important difference (MCID) of at least one grade reduction in the MAS; see paragraph 6.10 below for further details. The PSCR stated that the current/proposed restriction follows the historical MAS coding convention; whereas the clinical trial was aligned with the coding conventions of the 'derived MAS'. This change means that patients who receive a MAS score of 1+ and were previously coded as 1.5 are now coded as 2, with subsequent MAS scores increasing by a value of 1 (see Table 2). The ESC noted that a decrease of greater than one in the historical coding aligned with a decrease of at least 2 in the 'derived MAS' coding convention which was used in the trial.

2.10 The ESC questioned which coding convention was most commonly used in clinical practice, noting that the two coding conventions were not presented in the submissions for Dysport® (Item 6.02) or BOTOX® (Item 7.02) for lower limb spasticity. The pre-PBAC Response claimed that data is not available for which coding convention is most commonly used in clinical practice, but suggested that physicians could effectively switch between the two conventions.

Table 2: Description of the Modified Ashworth Scale (MAS)

MAS score	Historical code	Derived code	Description
0	0	0	Normal tone, no increase in muscle tone
1	1	1	Slight increase in muscle tone, manifested by a catch or by minimal resistance at the end of the range of motion (ROM) when the affected part(s) is (are) moved in flexion or extension
1+	1.5	2	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM
2	2	3	More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved
3	3	4	Considerable increase in muscle tone, passive movement difficult
4	4	5	Affected part(s) rigid in flexion or extension

Source: Table 2.26, p68 of the submission and Table 1, p5 of the PSCR

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

3 Background

Registration status

3.1 TGA status: Dysport® was TGA registered on 16 March 2018 for "symptomatic treatment of focal spasticity affecting the upper limbs in adults". It was previously approved for "spasticity of the upper limb in adults following a stroke".

3.2 The PBAC noted that the TGA approved Dysport® for the treatment of focal spasticity of the upper limbs due to any aetiology, on the basis that the underlying cause of spasticity would not have a major effect on the utility of the treatment.

3.3 Other approved indications include focal spasticity of the lower limbs in adults and in children, spasmodic torticollis, blepharospasm, hemifacial spasm and glabellar lines.

Previous PBAC considerations

3.4 The PBAC recommended Dysport® for the treatment of upper limb spasticity following a stroke in November 2007. Dysport® is also PBS listed for treatment of spasmodic torticollis, blepharospasm and hemifacial spasm in adults.

3.5 This was the first submission to extend the Dysport® listing to include upper limb spasticity following an acute event. This extension of restriction aligns with the RMSANZ request, considered by the PBAC in July 2018, to facilitate the 'expansion of funded conditions to include muscle overactivity of any aetiology'.

3.6 This request to remove the limit of four treatment periods also aligned with the RMSANZ request.

3.7 The RMSANZ also requested to 'reduce the time limit for first injection of post-stroke upper limb spasticity to less than three months'. The submission did not request to reduce this time limitation.

3.8 A summary of the November 2007 PBAC considerations for Dysport® for upper limb spasticity in adult patients following stroke is presented in Table 3.

3.9 In May 2018, DUSC provided advice to the PBAC in a review of utilisation of botulinum toxin supplied through the PBS for treatment of spasticity in patients with cerebral palsy or following a stroke, and for spasmodic torticollis, blepharospasm and hemifacial spasm (Item 10.06 July 2018). This followed the above mentioned request from the RMSANZ to the PBAC to review a perceived inequity of access for patients to botulinum toxin treatments in the current PBS restrictions.

Table 3: Summary of the November 2007 PBAC submission for Dysport for upper limb spasticity in adult patients due to acute injury

	November 2007 Dysport submission
Indication	Treatment of moderate to severe spasticity of the upper limb in adults following a stroke, as second line therapy when standard management has failed or as an adjunct to physical therapy.
Evidence	One new trial (097) conducted in Australia, supportive evidence from three RCTs (Study 016, Study 049, Bhakta 2000) presented previously and additional two meta-analyses (Francis 2004, Cardoso 2005).
Outcome	Changes in QoL from weeks 0 to 20, based on trial (097). The PBAC noted the objective of the trial was to show the change in spasticity was functionally relevant to patients. Although the difference in mean QoL between placebo and Dysport was not statistically different, disease specific functional measures were positive for Dysport. The PBAC noted Dysport treatment resulted in more patients with reduction in MAS ≥ 1 at week 20 and agreed this change was significant. The PBAC considered the relevance of MAS improvement was supported by GAS and GAB, which the PBAC also considered clinically important.
Economic evaluation	Trial based CEA. Incremental cost per extra responder (MAS change greater than 1 in at least one joint at Week 20) was estimated as ≤ $15k. PBAC noted that the results of 097 could not be used to extrapolate to a CUA because there was no improvement in QoL, given wide variation in baseline QoL scores. Results were very sensitive to definition of MAS response, using MAS ≥ 1, the ICER reduced to $[redacted], and using MAS ≥ 2, the ICER increased to $[redacted]. The PBS response criteria adopted was MAS > 1 in ≥ 1 joint after two treatment cycles. The PBAC considered that although there was uncertainty in the size or sustainability of the functional outcome and the impact of this on quality of life and subsequently the cost-effectiveness that this could be mitigated by RSA. Several RSA options were proposed to minimise budget impact in excess of $8 million per annum.
PBAC decision	Recommended based on an acceptable cost-effectiveness. A restriction was applied on the maximum number of treatments authorised as 4 per upper limb and per lifetime.

Abbreviations: CEA=cost-effectiveness analysis; CUA=cost-utility analysis; GAB=Global Assessment of Benefit; GAS=Goal Attainment Scaling; ICER=incremental cost-effectiveness ratio; MAS=Modified Ashworth Scale; PBAC=Pharmaceutical Benefits Advisory Committee; PBS=Pharmaceutical Benefits Scheme; QoL=quality of life; RCT=randomised controlled trial; RSA=risk sharing arrangement

4 Population and disease

4.1 The submission estimated that around 75% of patients with physical disability after severe TBI will develop spasticity that necessitates specific treatment[1], and of these, approximately one-third may require treatment with botulinum toxin.

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.

[1] Royal College of Physicians, 2018. Spasticity in adults: management using botulinum toxin. National guidelines 2018.

4.3 The main role of botulinum toxin injections in limb spasticity is to produce temporary relaxation of the targeted muscles, allowing them to be stretched more easily, thus providing a window of opportunity for physical therapy.

4.4 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. This does not preclude Dysport® from being used without physical therapy. Standard management includes physiotherapy and/or oral spasticity agents.

4.5 Dysport® is given by intramuscular injection directly into each of the affected muscles. The maximum recommended dose for spasticity affecting the upper limbs in adults is 1000U in a single treatment session. Repeat Dysport® treatment should be administered when the effect of a previous injection has diminished, but no sooner than 12 weeks after the previous injection. If treatment is required in the upper and lower limbs during the same treatment session, the dose of Dysport® to be injected in each limb should be tailored to the individual needs, without exceeding a total dose of 1500U.

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

5 Comparator

5.1 The submission appropriately nominated placebo or best supportive care as the comparator on the justification that there are no medicines currently listed on the PBS for upper limb focal spasticity due to a non-stroke event. The comparator of best supportive care or standard management (physiotherapy, orthoses ± oral anti-spasticity drugs) was previously accepted by the PBAC in the Dysport® November 2007 resubmission.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician outlined the impact of focal spasticity on a patient's quality of life and capacity for recovery from acute events. The clinician highlighted the benefit attained with each round of treatment, when the drug would be used in practice, and that the goals of therapy remained the same despite the cause of the spasticity. The clinician also addressed other matters in response to the Committee's questions. The PBAC considered that the hearing was informative as it provided a clinical perspective on the functional goals and clinical benefits of treatment.

Consumer comments

6.2 The PBAC noted and welcomed the input from two health care professionals via the Consumer Comments facility on the PBS website. The comments described the

benefits of treatment with botulinum toxin for patients following an acute event other than stroke and how more than four doses are used in patients who continue to respond to treatment.

Clinical trials

6.3 The submission was based on:

- Study 145: a RCT comparing Dysport® to placebo over one treatment cycle: (N=243);
- Study 148: an open-label extension study of Study 145 in which patients received Dysport® for up to four additional treatment cycles (N=254): Study 148; and
- Smith 2000 (N=21) and Lam 2012 (N=55): two smaller supportive RCTs comparing Dysport® to placebo.

6.4 A subgroup of patients with TBI from Study 145 (n=23) was used to support the clinical claim.

6.5 The submission included one further small supportive trial (Akulov 2015). As this trial evaluated the efficacy of Dysport® injections under electromyographic (EMG) control versus control patients administered Dysport® injections without EMG control, it was excluded during the evaluation since the trial does not report results for the comparison of interest of Dysport® versus placebo.

6.6 Details of the trials presented in the submission are provided in Table 4.

Table 4: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Main trial		
Study 145	A phase 3, multicentre, prospective, double blind, randomised, placebo controlled study, assessing the efficacy and safety of Dysport® intramuscular injections used for the treatment of upper limb spasticity in adult subjects with spastic hemiparesis due to stroke or traumatic brain injury.	April 2014
	Gracies J-M, Brashear A, Jech R et al. Safety and efficacy of abobotulinumtoxinA for hemiparesis in adults with upper limb spasticity after stroke or traumatic brain injury.	*LancetNeurol* 2015; 14: 992-1001.
	O'Dell M, Brashear A, Walker H et al. AbobotulinumtoxinA (Dysport®) in the treatment of adult patients with upper-limb spasticity due to traumatic brain injury.	PM and R. Conference: 2015 Annual Assembly of the American Academy of Physical Medicine and Rehabilitation. Boston, MA United States. Conference Publication: 7 (9 SUPPL. 1) (pp S103), 2015
Study 148 (extension study)	A phase 3, multicentre, prospective, open label, extension study to assess the long-term safety and efficacy of repeated treatment of Dysport intramuscular injections used for the treatment of upper limb spasticity in adult subjects with spastic hemiparesis due to stroke or traumatic brain injury.	December 2015
	Gracies J-M, O'Dell M, Vecchio M et al. Effects of repeated abobotulinumtoxinA injections in upper limb spasticity.	*Muscle Nerve* 2018; 57: 245-254.
Supportive trials		
Smith 2000	Smith SJ, Ellis E, White S et al. A double-blind placebo-controlled study of botulinum toxin in upper limb spasticity after stroke or head injury.	*Clinical Rehabilitation* 2000; 14: 5-13.
Lam 2012	Lam K, Lau KK, So KK et al. Can botulinum toxin decrease carer burden in long-term care residents with upper limb spasticity? A randomized controlled study.	*Journal of the American Medical Directors Association* 2012; 13(5): 447-484.

Source: Table 2.3, pp43-45 of the submission.

6.7 The key features of the direct randomised trials are summarised in Table 5.

Table 5: **Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Dysport® vs. placebo						
Study 145	243	R, DB, MC 12-24 weeks	Low	Post-stroke (≈90%) or TBI (≈10%) ≥ 6 months previously; MAS ≥ 2 toxin naïve, MAS ≥ 3 non-toxin naïve	1º: change in MAS at 4 weeks 2º: PGA, DAS	Base case: MAS responder[a] Sensitivity: PGA[b] and DAS responders[c]
Study 148	254	R, OL, MC 12 months	High		1º: Long term safety Other: Long term efficacy	Not used
Smith 2000	21	R, DB 6-12 weeks	Low	Post-stroke (≈90%) or TBI (≈10%) ≥ 12 months previously	1º: change in MAS, PROM and AROM at 6 weeks.	Not used
Lam 2012	55	R, DB 24 weeks	Low	ULFS from "brain' causes MAS > 2	1º: 4-point improvement in CBS at 6 weeks 2º: GAS, MAS, PROM	Not used

Abbreviations: DB=double blind; MC=multi-centre; OL=open label; R=randomised; AROM= active range of motion; CBS=Carer Burden Scale; DAS=Disability Assessment Scale; GAS=Goal Attainment Scaling; MAS=modified Ashworth Scale; PGA=Physician's Global Assessment; PROM= passive range of motion; TBI=traumatic brain injury; ULFS=upper limb focal spasticity.

[a] MAS reduction from baseline ≥ 1

[b] PGA score ≥ 1

[c] MAS reduction from baseline ≥ 1

Source: compiled during the evaluation.

6.8 The ESC noted that subgroups of patients with non-stroke spasticity in the included trials were small. The majority of patients (90.3%) in Study 145 had upper limb focal spasticity due to stroke, with 9.7% having spasticity due to TBI. In Smith 2000, spastic hemiplegia was due to TBI in two patients (9.5%), and due to stroke in 19 patients (90.5%). It was uncertain how many patients in Lam 2012 had upper limb spasticity due to each specific cause, as the quoted cause was "brain" for all patients. No evidence was presented in the submission for patients with upper limb focal spasticity due to other aetiologies, such as spinal cord injury, hypoxia or infection. The PSCR reiterated the difficulties associated with recruiting patients who have suffered from other forms of acute event, and the currently unmet medical need for this small, but equally disabled, group. The ESC considered that patients with spasticity due to differing aetiologies were likely to have different prospects for rehabilitation and the goals of treatment were likely to vary, and that this would also affect the determination of cost effectiveness. The pre-PBAC Response maintained that the benefits of Dysport® could be applied equally to stroke and non-stroke populations, as evidenced by improvement in efficacy endpoints in Study 145 and Study 148.

Comparative effectiveness

6.9 The submission's clinical claims were based on change in spasticity measured by the MAS score and supported by functional outcomes including Physician Global Assessment (PGA) responders and Disability Assessment Scale (DAS) responders.

6.10 The MAS is a common outcome reported in trials of botulinum toxin and spasticity, and it has been presented in past PBAC submissions. The 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. PGA and DAS are subjective functional outcomes. The PGA is an investigator rated response to treatment after injection of treatment. The DAS is an upper-limb specific tool that assessed four domains of disability associated with passive functioning (hygiene, dressing, limb position and pain).

6.11 The submission nominated a minimal clinically important difference (MCID) of an at least one grade reduction in the MAS (MAS ≥ 1), using the 'derived MAS' at Week 4. The ESC noted that the PBAC had previously accepted a decrease in MAS of at least one point in at least one joint at Week 20 (using the historical MAS coding convention) to be clinically significant when supported by several significant changes in functional outcomes (Goal Attainment Scaling score (GAS) and Global Assessment of Benefit (GAB) score) in upper limb focal spasticity post stroke (November 2007, Dysport® public summary document (PSD)). The ESC noted that a decrease in MAS > 1 using the historical coding convention aligned with a decrease of MAS ≥ 2 when using the 'derived MAS' coding convention, which was used in the key trial. The PBAC considered a MAS ≥ 2 using the 'derived MAS', when accompanied by other functional outcomes such as goal attainment, would likely represent a clinically meaningful response.

6.12 Table 6 summarises the MAS outcomes in the primary targeted muscle group following a single treatment from Study 145. The time point for assessment of MAS outcomes in Study 145 was Week 4. The economic evaluation used the proportion of responders at Week 12 in its base case analysis.

Table 6: Results of MAS outcomes from Study 145

	ITT population			TBI subgroup		
	Dysport 1000U	**Dysport 500U**	**Placebo**	**Dysport 1000U**	**Dysport 500U**	**Placebo**
	N=79	**N=80**	**N=79**	**N=6**	**N=8**	**N=9**
Primary outcome: change from baseline in MAS score in the PTMG at Week 4						
Baseline, mean (SD)	3.9 (0.4)	3.9 (0.5)	3.9 (0.4)	4 (0)	3.8 (0.5)	4 (0)
Week 4, mean (SD)	2.6 (1.2)	2.7 (1.0)	3.7 (0.7)	2.8 (1.2)	3 (0.9)	3.8 (0.4)
Change from baseline in MAS at Week 4						
Mean change (SD)	-1.4 (1.1)	-1.2 (1.0)	-0.3 (0.6)	-1.2 (1.2)	-0.8 (0.7)	-0.2 (0.4)
LS mean (95% CI)	**-1.4 (-1.6, -1.2)**	**-1.2 (-1.4, 1.0)**	**-0.3 (-0.5, -0.1)**	-	-	-
Comparison to placebo						
LS mean (95% CI)	**-1.1 (-1.4, -0.8)**	**-0.9 (-1.2, -0.6)**	NA	**-0.9 (-1.8, -0.1)**	-0.5 (-1.3, 0.3)	NA
p-value	**<0.0001**	**<0.0001**	NA	-	-	NA
MAS responders at Weeks 4 and 12 (reduction ≥ 1 or more)						
Responders at Week 4, n (%)	62 (78.5%)	59 (73.8%)	18 (22.8%)	4 (66.7%)	5 (62.5%)	2 (22.2%)
RD (95% CI)	**0.56 (0.43. 0.69)**	**0.51(0.38, 0.64)**	NA	0.44 (-0.02, 0.91)	0.40 (-0.03, 0.83)	NA
p-value (versus placebo)	**<0.0001**	**<0.0001**	NA	0.09	0.09	NA
Responders at Week 12, n (%)	38 (48.1%)	34 (42.5%)	11 (13.9%)	1 (16.7%)	4 (50.0%)	1 (11.1%)
RD (95% CI)	**0.34 (0.21, 0.48)**	**0.29 (0.15, 0.42)**	NA	0.06 (-0.31, 0.42)	0.39 (-0.01, 0.79)	NA
p-value (versus placebo)	**<0.0001**	**<0.0001**	NA	0.76	0.08	NA
MAS responders at Weeks 4 and 12 (reduction ≥ 2 or more)						
Responders at Week 4, n (%)	29 (36.7%)	28 (35.0%)	3 (3.8%)	-	-	-
RD (95% CI)	**0.33 (0.22, 0.44)**	**0.31 (0.20, 0.42)**	NA	-	-	-
Responders at Week 12, n (%)	14 (17.7%)	8 (10.0%)	3 (3.8%)	-	-	-
RD (95% CI)	**0.14 (0.05, 0.24)**	0.06 (-0.02, 0.14)	NA	-	-	-

Bolded values reached statistical significance. Italics indicate results estimated during the evaluation using RevMan v5.3, and STATA 15.
Abbreviations: LS=least squares; MAS=modified Ashworth scale; NA=not applicable; NR=not reported; PTMG=primary targeted muscle group; TBI=traumatic brain injury, RD=risk difference.

Source: Table 2.31, Table 2.33, pp.75-78 of the submission; Table 3.6, p132 of the submission.

6.13 The mean MAS reductions at Week 4 were statistically significantly higher in patients treated with Dysport® compared to placebo in the intention to treat (ITT) population. For patients treated with Dysport® 1000U the result was clinically significant, as it exceeded the nominated MCID of reduction in MAS ≥ 1.

6.14 In the subgroup of TBI patients, the mean reduction in the MAS score at Week 4 was not significantly different for Dysport® 500U versus placebo. The mean MAS reduction in Dysport® 1000U compared to placebo was statistically significant, but not clinically significant, as it did not meet the MCID nominated by the submission. These subgroup analyses were *post-hoc* analyses of Study 145, and were not powered to detect statistical significance.

6.15 In the ITT population, both Dysport® treatment groups were significantly more effective than placebo in terms of the proportion of patients attaining a MAS response at Week 4.

6.16 The results for changes from baseline in MAS scores from Lam 2012 were consistent with those from Study 145. However, in Smith 2000, the reduction in the MAS score was not statistically significant for most of the Dysport® treatment groups compared to placebo.

6.17 Table 7 presents incremental benefit results from the PSCR, which were re-coded using the historical MAS coding convention.

Table 7: MAS outcomes in Study 145 recoded for historical MAS coding convention – incremental benefit

Responders at Week 12 (1000U), ITT population	MAS ≥ 1	MAS > 1	MAS ≥ 2
'derived MAS' coding convention, RD (95% CI)	35.3% (21.5, 49.1)*	NA	14.4% (4.6, 24.2)
Historical coding convention, RD (95% CI)	35.4% (21.7, 49.0)	13.1% (3.5, 22.7)	3.9% (-2.7, 10.6)

CI = confidence interval; ITT = intention to treat; MAS = Modified Ashworth Scale; NA = not applicable; RD = risk difference

* Discrepancy with RD in Table 6 of 0.33 is due to the population used. Table 6 used ITT (N= 79), Table 7, the number of patients observed at Week 12 (N = 76)

Source: Table 2, p5 PSCR

6.18 Although the proportion of MAS responders (MAS ≥ 1 and MAS > 1) was statistically significantly higher for patients who received 1000U Dysport® compared to placebo using the historical coding convention, the PBAC noted that no data was provided for the mean change in MAS or for the subgroup of patients who had spasticity due to a TBI.

6.19 The cost-effectiveness analyses presented in the submission were based on patients with an improvement in MAS ≥ 1 using the 'derived MAS' coding convention (i.e. 35.3%); the PSCR presented revised cost-effectiveness analyses based on patients with an improvement in MAS > 1 and using the historical MAS coding convention (i.e. 13.1%), which was consistent with that presented in November 2007.

6.20 The PSCR presented responder analyses for patients from Study 148 who received treatment Cycles 3 and 4. Results were presented using both the historical and 'derived MAS' coding conventions – see Table 8.

Table 8: Analysis of continued responders, Study 148

	'derived MAS' convention (MAS ≥ 1)		Historical convention (MAS > 1)	
	Cycle 3	Cycle 4	Cycle 3	Cycle 4
Patients who responded in ≥ 1 of the first two treatment cycles	73/96 (76.0%)	22/27 (81.5%)	20/29 (69.0%)	0/3 (0)
Patients who did not respond in the first two treatment cycles	15/59 (25.4%)	12/30 (40.0%)	18/126 (14.3%)	9/54 (16.7%)

MAS = Modified Ashworth Scale
Source: Table 4, p5 of the PSCR

6.21 The ESC were concerned, given that the stopping criterion applies after the first two cycles, that, when the 'derived MAS' coding was used:

- there was a proportion of patients who would continue to receive Dysport® who would not continue to respond; and
- there could be patients who would benefit from continuing treatment who would not receive it as they would have met the stopping rule criteria.

6.22 Table 9 summarises the outcomes of functional measures from Study 145 and Lam 2012. The time point for assessment of functional outcomes in Study 145 was Week 4 and in Lam 2012, Week 6.

Table 9: Functional measure results: Study 145 - PGA and DAS; Lam 2012 - CBS and GAS

Study 145			
	Dysport 1000U	**Dysport 500U**	**Placebo**
	N=79	**N=80**	**N=79**
PGA at Week 4 - ITT			
Mean (SD)	1.8 (1.1)	1.4 (1.1)	0.6 (1.0)
LS mean (95% CI)	1.8 (1.6, 2.1)	1.4 (1.1, 1.6)	0.7 (-0.5, 1.0)
LS mean (95% CI) versus placebo	**1.1 (0.8, 1.4)**	**0.6 (0.3, 1.0)**	**NA**
p-value (versus placebo)	**<0.0001**	**0.0003**	**NA**
Subgroup analysis: TBI patients			
N	6	8	9
Mean (SD)	1.5 (0.5)	1.5 (1.2)	0.6 (1.2)
PGA responders (score ≥ +1 or more)			
Responders, n (%)	6 (100%)	7 (87.5%)	3 (33.3%)
Change from baseline in DAS at Week 4 - ITT			
Baseline, mean (SD)	2.5 (0.5)	2.6 (0.5)	2.6 (0.5)
Week 4, mean (SD)	1.8 (0.7)	1.9 (0.8)	2.1 (0.8)
Change from baseline in DAS at Week 4			
Mean change (SD)	-0.7 (0.7)	-0.7 (0.8)	-0.5 (0.7)
LS mean (95% CI)	-0.7 (-0.8, 0.5)	**-0.6 (-0.8, -0.4)**	-0.5 (-0.6, 0.3)
Comparison to placebo			
LS mean (95% CI)	-0.2 (-0.4, 0.00)	-0.1 (-0.4, 0.1)	NA
p-value	0.0772	0.2560	NA
DAS responders at Weeks 4 and 12 (reduction ≥ 1 or more) - ITT			
Responders at Week 4, n (%)	49 (62.0%)	40 (50.0%)	31 (39.2%)
Risk difference (95% CI)	**0.23 (0.08. 0.38)**	0.11 (-0.05, 0.26)	NA
p-value (versus placebo)	**0.0018**	0.1279	NA
Responders at Week 12, n (%)	44 (55.7%)	33 (41.3%)	26 (32.9%)
Risk difference (95% CI)	**0.23 (0.08, 0.39)**	0.08 (-0.07, 0.23)	NA
p-value (versus placebo)	**0.0004**	0.1053	NA
Subgroup analysis: TBI patients			
N	6	8	9
Responders at Week 4, n (%)	5 (83.3%)	5 (62.5%)	2 (22.2%)
Lam 2012			
	Dysport[a]		**Placebo**
	N=30		**N=25**
Carer Burden Scale (CBS) at Week 6			
Achieving 4-point improvement in CBS at Week 6, n (%)	18 (60.0%)		2 (8.0%)
p-value (versus placebo)	**<0.001**		NA
Change from baseline in Goal Attainment Scaling (GAS) at Week 6			
Baseline, mean (SD)	37.93 (0.64)		38.0 (0.0)
Week 6, mean (SD)	61.67 (12.05)		49.08 (14.95)
Change from baseline in GAS at Week 6			
Mean change (SD)	23.73 (12.08)		11.08 (14.95)
Comparison to placebo			
Difference (95% CI)	**12.65 (5.34, 19.96)**		NA
p-value	**0.001**		NA

Bolded values reached statistical significance.

Abbreviations: CBS=Carer Burden Scale; DAS=Disability Assessment Scale; GAS=Goal Attainment Scaling; LS=least squares; NA = not applicable; PGA=Physician's Global Assessment; PTT=principal target of treatment; TBI=traumatic brain injury.

[a] The maximum total dose was 1000 units for one patient.

Source: Table 2.31, Table 2.33, Table 2.34, Table 2.35, pp.75-80 of the submission and Table 19, p58 of CSR for Study 145; Table 5, p451 of Lam 2012 publication.

6.23 The mean PGA scores at Week 4 were statistically significantly higher in patients treated with Dysport® compared to placebo in the ITT population of Study 145; however, changes in DAS for the principal target of treatment were not significantly different. The PBAC considered that the subgroup analyses of patients with TBI were difficult to assess due to small patient numbers.

6.24 Quality of life outcomes for the ITT population from Study 145 are presented in Table 10. There were no statistically significant differences between treatment groups for any of the SF-36 or EQ-5D-5L domains.

Table 10: Results of quality of life outcomes in Study 145, mean change from baseline at Week 12

	ITT population		
	Dysport 1000U	Dysport 500U	Placebo
	N=74	N=73	N=74
SF-36, mean change from baseline (SD)			
Mental component	-0.00 (11.06)	0.48 (9.12)	1.28 (8.67)
Physical component	1.16 (6.02)	0.68 (6.03)	1.77 (7.53)
EQ-5D-5L, mean change from baseline (SD)			
Anxiety depression	0.1 (0.8)	-0.1 (0.9)	-0.3 (1.0)
Mobility	0.1 (0.7)	0.0 (1.0)	0.0 (0.9)
Pain/discomfort	0.0 (0.8)	-0.3 (0.9)	-0.2 (0.8)
Self-care	0.2 (0.9)	-0.2 (0.9)	0.0 (0.8)
Usual activities	0.1 (0.9)	-0.1 (1.0)	-0.2 (0.9)
EQ-5D VAS	2.9 (15.9)	2.4 (18.9)	2.0 (19.6)

SD = standard deviation; VAS = visual analogue scale
Source: Supplementary Table 3, Appendix to Gracies (2015).

6.25 A series of correlation analyses performed in the submission demonstrated that although there was some relationship between MAS and functioning scales, there was generally a lack of significant associations between MAS and EQ-5D-5L derived utility.

Comparative harms

6.26 The proportion of patients reporting at least one treatment emergent adverse event in the ITT population of Study 145 was significantly higher with Dysport® (1000U = 42%; 500U = 44.4%) compared to placebo (25.9%); however, the majority were mild in intensity. The incidence of any adverse event, serious adverse events, discontinuations due to treatment emergent adverse events and deaths were similar between the Dysport® and placebo treatment groups. In Study 145, the most frequently reported adverse events were nasopharyngitis and muscular weakness. The ESC noted that the type of treatment emergent adverse events associated with Dysport® were limited, but higher than in the placebo group. In addition, the ESC noted that patients receiving standard of care in practice would not receive a placebo injection.

Benefits/harms

6.27 A summary of the comparative benefits and harms for Dysport® versus placebo is presented in Table 11.

Table 11: Summary of comparative benefits and harms for Dysport® and PBO

Benefits							
Continuous outcome: change from baseline to Week 4 in MAS in the PTMG							
	Dysport			**PBO**			**Mean difference* (95% CI): Dysport vs. PBO**
	N	**Mean Δ baseline**	**SD**	**N**	**Mean Δ baseline**	**SD**	
Study 145: ITT							
Dysport 1000U	79	-1.4	1.1	79	-0.30	0.6	**-1.1 (-1.4, -0.8)**
Dysport 500U	80	-1.2	1.0				**-0.9 (-1.2, -0.6)**
Study 145: TBI subgroup							
Dysport 1000U	6	-1.2	1.2	9	-0.20	0.4	**-0.9 (-1.8, -0.1)**
Dysport 500U	8	-0.8	0.7				-0.5 (-1.3, 0.3)
Dichotomous outcome: MAS responder (Δ≥1) at Week 4							
Trial	**Dysport n/N**	**PBO n/N**	**RR (95% CI)**		**Event rate/100 patients***		**RD (95% CI)**
					Dysport	**PBO**	
Study 145: ITT							
Dysport 1000U	62/79	18/79	**3.44 (2.26, 5.25)**		78.5	22.8	**0.56 (0.43, 0.69)**
Dysport 500U	59/80		**3.24 (2.11, 4.96)**		73.8		**0.51 (0.38, 0.64)**
Study 145: TBI subgroup							
Dysport 1000U	4/6	2/9	3.00 (0.78, 11.54)		66.7	22.2	0.44 (-0.02, 0.91)
Dysport 500U	5/8		2.81 (0.74, 10.69)		62.5		0.40 (-0.03, 0.83)
Continuous outcome: PGA at Week 4							
	Dysport			**PBO**			**Mean difference* (95% CI): Dysport vs. PBO**
	N	**Mean**	**SD**	**N**	**Mean**	**SD**	
Study 145: ITT							
Dysport 1000U	79	1.8	1.1	79	0.6	1.0	**1.1 (0.8, 1.4)**
Dysport 500U	80	1.4	1.1				**0.6 (0.3, 1.0)**
Study 145: TBI subgroup							
Dysport 1000U	6	1.5	0.5	9	0.6	1.2	NR
Dysport 500U	8	1.5	1.2				NR
Continuous outcome: change from baseline to Week 4 in DAS							
	Dysport			**PBO**			**Mean difference* (95% CI): Dysport vs. PBO**
	N	**Mean Δ baseline**	**SD**	**N**	**Mean Δ baseline**	**SD**	
Study 145: ITT							
Dysport 1000U	79	-0.7	0.7	79	-0.5	0.7	-0.2 (-0.4, 0.00)
Dysport 500U	80	-0.7	0.8				-0.1 (-0.4, 0.1)
Harms: TEAEs							
	Dysport n/N	**PBO n/N**	**RR (95% CI)**		**Event rate/100 patients***		**RD (95% CI)**
					Dysport	**PBO**	
Study 145: ITT							
Dysport 1000U	34/81	21/81	**1.62 (1.03, 2.54)**		42.0	25.9	**0.16 (0.02, 0.30)**
Dysport 500U	36/81		**1.71 (1.10, 2.67)**		44.4		**0.19 (0.04, 0.33)**
Study 145: TBI subgroup							
Dysport 1000U	3/6	2/9	2.25 (0.52, 9.70)		50.0	22.2	0.28 (-0.21, 0.76)
Dysport 500U	2/8		1.13(0.20, 6.24)		25.0		0.03 (-0.38, 0.43)

Abbreviations: DAS=Disability Assessment Scale; MAS=modified Ashworth scale; RD = risk difference; RR = risk ratio; PGA=Physician's Global Assessment; PTMG=primary targeted muscle group; TBI=traumatic brain injury; TEAE=treatment emergent adverse event, NR=not reported.

*Median duration of follow-up: Study 145 = 13.0-13.6 weeks.

Source: compiled during the evaluation based on efficacy results reported in the submission.

6.28 On the basis of direct evidence presented by the submission, treatment with one dose of Dysport® 1000U compared to placebo in the:

A) ITT population of Study 145 resulted in a:

- 1.1 point reduction in MAS score from baseline in the primary targeted muscle group at Week 4.
- 1.1 point mean difference in PGA score at Week 4.

B) TBI subgroup of Study 145 resulted in a:

- 0.9 point reduction in MAS score from baseline in the primary targeted muscle group at Week 4.

6.29 On the basis of direct evidence presented by the submission, treatment with one dose of Dysport® 500U compared to placebo in the:

ITT population of Study 145 resulted in a:

- 0.9 point reduction in MAS score from baseline in the primary targeted muscle group at Week 4.
- 0.6 point mean difference in PGA score at Week 4.

6.30 On the basis of direct evidence presented by the submission (ITT population of Study 145), for every 100 patients treated with one dose of Dysport® 1000U in comparison to placebo:

- Approximately 56 additional patients would have MAS response (change ≥ 1) at Week 4.
- Approximately 16 additional patients would experience a treatment emergent adverse event.

6.31 On the basis of direct evidence presented by the submission (ITT population of Study 145), for every 100 patients treated with one dose of Dysport® 500U in comparison to placebo:

- Approximately 51 additional patients would have MAS response (change ≥ 1) at Week 4.
- Approximately 19 additional patients would experience a treatment emergent adverse event.

Clinical claim

6.32 The submission claimed that the benefits of Dysport® treatment extended beyond its current listing for upper limb focal spasticity following stroke. The submission considered that Dysport® was superior in terms of effectiveness compared to placebo/best supportive care in the treatment of upper limb focal spasticity following non-stroke acute events, as represented by the subgroup of patients with TBI.

6.33 The ESC considered that the benefit in treating upper limb focal spasticity due to non-stroke acute events was uncertain as:

- These patients were poorly represented in the trial evidence. Ten percent of patients from Study 145 had upper limb spasticity following a TBI, but no evidence was presented for other aetiologies such as hypoxia or infection.
- The subgroups of TBI patients from Study 145 (n = 23) and Smith 2000 (n = 2) were small and analyses were *post-hoc* and not powered to detect statistical significance.
- The benefit for Dysport® versus placebo in terms of change in MAS and MAS responders was defined using the 'derived MAS' coding convention. Although some MAS responder data was presented in the PSCR which was re-coded using the historical coding convention, no information was presented for the TBI subgroup.

6.34 The PBAC considered that the claim that Dysport® was superior in terms of comparative effectiveness to standard of care/placebo in the treatment of patients with upper limb focal spasticity following a non-stroke acute event was not adequately supported by the data.

6.35 The submission did not make a claim regarding the safety of Dysport® compared to placebo in the treatment of upper limb focal spasticity following an acute event. The ESC noted that the PBAC had previously accepted that Dysport® was associated with greater toxicity compared to standard management (Dysport® PSD, November 2007 PBAC).

6.36 The PBAC considered that Dysport® was inferior in terms of comparative safety compared to standard of care/placebo.

Economic analysis

6.37 The submission presented a cost effectiveness analysis, in the form of a cost per responder, as was previously accepted by the PBAC (November 2007, Dysport® PSD). In November 2007 the cost per responder (defined as a change in MAS of greater than one (using the historical MAS coding convention), in at least one joint at 20 weeks) for Dysport® in the treatment of upper limb spasticity following a stroke was less than $15,000.

6.38 The aim of the submission's economic evaluation was to estimate the cost effectiveness of Dysport® in the treatment of upper limb focal spasticity following any acute event. As efficacy outcomes in the model were based on the ITT results from Study 145, the estimated cost effectiveness was primarily driven by outcomes for patients post-stroke. As previously discussed, 90% of the patients in Study 145 were post-stroke, with approximately 10% suffering from spasticity due to a TBI. The applicability of the modelled results to the additional population for whom listing was sought was therefore uncertain.

6.39 The base case defined a MAS responder using the 'derived MAS' coding convention as patients with ≥ 1 MAS change from baseline to 12 weeks. As noted, this definition differed from the requested restriction, from the clinical outcome which assessed

MAS change at 4 weeks, and from the definition used in economic evaluation of Dysport® in the treatment of upper limb spasticity following a stroke, in which a responder was defined, using the historical MAS coding convention, as having a mean change in MAS of greater than one in at least one of the joints at Week 20 (November 2007, Dysport® PSD).

6.40 Individual patient data from Study 148 suggested that patients would receive 3.86 treatment cycles of Dysport®. The submission, assuming a non-responder rate of 33.6% at Week 12 and accounting for non-responders stopping treatment after two injections based on PBS stopping criteria, estimated that patients would receive an average of 3.24 treatment cycles (base case).

6.41 There was a mismatch between the 3.24 treatment cycles assumed for costing and the single dose Study 145 from which the incremental responders were derived. The submission presumably relied on data from the extension open-label Study 148 to support the maintenance of treatment effect over repeat Dysport® dosing. However, detailed responder analyses (estimating response in initial responders) were not presented in the submission to verify continued response rates. Responder analyses, provided in the PSCR and presented in Table 8 above, demonstrated that the probability of response in the later treatment cycles was greater in those who responded in the first two treatment cycles.

6.42 The dose per treatment was assumed to be 999U (i.e. 1.998 vials of the 500U dose form). This was based on the 1000U arm being the most frequently used dose in the open label extension Study 148. This appeared reasonable; 1000U is the maximum recommended dose per treatment cycle for upper limb spasticity.

6.43 The results of the economic evaluation, which were based on changes in the 'derived MAS', are presented in Table 12. The DPMQ for Dysport® 500U of $1,094.79 (based on PBS mark-ups from 1 July 2018), and the corrected MBS cost of $124.85 per administration, were used.

Table 12: Results of the economic evaluation

Component	Dysport	Placebo	Increment
Costs	$ [redacted] [a,b]	$ [redacted]	$ [redacted]
MAS responder (Δ ≥ 1) at 12 weeks	0.481	0.139	0.342[c]
Incremental cost/extra MAS responder (Δ ≥ 1) at 12 weeks			**$** [redacted]
Sensitivity analyses			
MAS responder (Δ ≥ 1) at 4 weeks	0.785	0.228	0.557
Incremental cost/extra MAS responder (Δ ≥ 1) at 4 weeks			$ [redacted]
MAS responder (Δ ≥ 2) at 12 weeks	0.177	0.038	0.139
Incremental cost/extra MAS responder (Δ ≥ 2) at 12 weeks			$ [redacted]

[a] The DPMQ of $1,094.79 for the Dysport® 500 unit (2 vials) preparation estimated during the evaluation using the requested AEMP of $523.75 per vial was used. This corresponds to the price in the July 2018 PBS schedule for the current post-stroke spasticity listing.
[b] The submission applied an administration cost of $124.95 for MBS item number 18360 for patients receiving Botox® for spasticity. The correct cost of $124.85 was used in the evaluation.
[c] In the submission, the risk differences have been calculated using the numbers of patients evaluated at Week 12. The risk differences have been recalculated using the "ITT" patient numbers as denominators in the evaluation.
Source: constructed during the evaluation.

The redacted table shows ICERs in the range of less than $15,000 per extra MAS responder to $15,000 - $45,000 per extra MAS responder.

6.44 The PSCR provided re-estimated cost-effectiveness calculations which were based on the historical MAS coding convention and in which a response was defined as a change in MAS of greater than 1 (see Tables 13 and 14), which was consistent with the November 2007 submission. These analyses indicated that 70.9% of patients did not respond to either of the first two treatment cycles (MAS > 1), and the response rate (as per Table 7 above) was estimated to be 13.1% (95% CI: 3.5, 22.7).

Table 13: Re-estimated inputs for cost per responder analysis

Average number of treatment cycles	3.86	Study 148
Total received before stopping rule applied	2	Proposed PBS restriction
Average number of cycles to be adjusted	1.86	-
Corrected number of cycles beyond stopping rule	0.56	At Week 12 in Study 148, after 2 treatment cycles, 186/258 (70.9%) of patients did not respond to either of the 2 treatment cycles, based on a MAS >1.
Corrected number of cycles with stopping rule	2.54	-
Corrected total cost per treatment	$[redacted]	Based on evaluators comments
Overall cost of treatment	$[redacted]	-

MAS = Modified Ashworth Scale
Source: Table 3, p5 of the PSCR

Table 14: Re-estimated cost per responder analyses based on historical coding convention for MAS

	Incremental cost	Incremental benefit	Cost per responder (95% CI)	Cost per responder Nov 2007 (95% CI)
MAS > 1 (base case)	**$[redacted]**	**0.131**	**$[redacted] ($[redacted], $[redacted])**	**$[redacted] ($[redacted], $[redacted])**
MAS ≥ 1	$[redacted]	0.354	$[redacted] ($[redacted], $[redacted])	$[redacted] ($[redacted], $[redacted])
MAS ≥ 2	$[redacted]	0.039	$[redacted] ($[redacted], NE)	$[redacted] ($[redacted], NE)
Sensitivity analyses				
3.24 cycles; MAS > 1 (historical coding)	$[redacted]	0.131	$[redacted] ($[redacted], $[redacted])	-
2.54 cycles; MAS ≥ 1 ('derived MAS' coding)	$[redacted]	0.353	$[redacted] ($[redacted], $[redacted])	-
2.54 cycles; MAS ≥ 2 ('derived MAS' coding)	$[redacted]	0.144	$[redacted] ($[redacted], $[redacted])	-

CI = confidence interval; MAS = Modified Ashworth Scale; NE = not estimable
Source: Table 3, p5 of the PSCR

6.45 The incremental cost per responder was sensitive to the definition of a MAS responder. Using data from Study 145 and Study 148 and a definition of response of MAS > 1 which was re-coded using the historical coding convention, resulted in a cost per responder analysis of $15,000 - $45,000. This was considerably higher than the corresponding cost per responder estimated in November 2007 of less than $15,000. The PSCR noted that the 95% confidence intervals were narrower, and sat inside those previously estimated. The ESC noted that the 2007 analyses were not updated to reflect 2018 costs. The pre-PBAC Response updated the 2007 cost per responder analyses to reflect the 2018 PBS costs for Dysport® and including analogous MBS costs, resulting in an incremental cost of less than $15,000 (95% CI: less than $15,000 to $75,000 - $105,000).

Drug cost/patient/course: $1,094.79 (Dysport® 1000U)

6.46 Assuming a Dysport® dose of 1000U, using the requested approved ex-manufacturer price for the 500U vial and PBS mark ups from 1 July 2018, the drug cost per patient per treatment cycle was estimated to be $1,094.79. This was the DPMQ for two 500U vials and was consistent with the July 2018 PBS DPMQ for post-stroke patients.

6.47 The DUSC considered that, on average, patients would receive three to four treatment cycles of botulinum toxin per lifetime (Item 10.6, July 2018, DUSC advice to PBAC on botulinum toxin).

6.48 The ESC considered that the number of treatment cycles per patient per lifetime for the proposed population was uncertain.

Estimated PBS usage & financial implications

6.49 The estimated extent of use and financial implications were considered by the DUSC.

6.50 A mixed approach was used to estimate the utilisation and financial impact of listing Dysport® for the treatment of upper limb spasticity following an acute event. The submission used an epidemiological approach to estimate Population 1, the number of patients with non-stroke related upper limb spasticity; and a market share approach to estimate Population 2, the increased lifetime use of Dysport® by patients with upper limb spasticity due to stroke and non-stroke events, due to the removal of the four treatment lifetime limit (see Table 15). Australian Institute of Health and Welfare (AIHW) hospital separation data for TBI, and data from the Australian Spinal Cord Injury Register were used to estimate the number of TBI and spinal cord injury patients respectively, who would be eligible for treatment. The incidence of 'other' patients (i.e. spasticity due to hypoxia, infection, surgery, etc.) was obtained from clinician feedback at a 2018 Australian advisory board meeting held by the Sponsor.

Table 15: Estimated use and financial implications

	2019	2020	2021	2022	2023	2024
Estimated extent of use						
Population 1 (new patients with non-stroke spasticity)						
Number of incident patients	[redacted]					
Number of prevalent patients	[redacted]					
Number of treatment cycles[a]	[redacted]					
Population 2 (effect of removal of lifetime limit)						
Additional number of treatment cycles (non-stroke)	[redacted]					
Increased number of treatment cycles (current stroke)	[redacted]					
Total number of treatment cycles	[redacted]					
Estimated financial implications of Dysport						
Population 1 (new patients with non-stroke spasticity)						
Cost to PBS/RPBS	$[redacted]					
Copayments	$[redacted]					
Net cost to PBS/RPBS	**$**[redacted]					
Population 2 (effect of removal of lifetime limit)						
Cost to PBS/RPBS	$[redacted]					
Copayments	$[redacted]					
Net cost to PBS/RPBS	**$**[redacted]					
Total cost to PBS/RPBS	**$**[redacted]					
Net financial implications						
Net cost to PBS/RPBS	$[redacted]					
Net cost to MBS	$[redacted]					
Net cost to PBS/RPBS/MBS	**$**[redacted]					

[a] Assuming 2.42 treatment cycles per patient per year; 3.13 treatment cycles per patient per lifetime as estimated by the submission.
Source: Table 4.12, Table 4.14, Table 4.15, Table 4.20; pp. 163-169 of the submission.

The redacted table shows that at Year 6 the estimated total number of treatment cycles was less than 10,000 per year, and the net cost to the PBS/MBS would be less than $10 million per year.

6.51 The total cost to government over the first six years of listing was estimated to be approximately $30 - $60 million. The key drivers of the results were uptake rates and prevalence of spasticity. DUSC considered the estimates may be under-estimated for the following reasons:

- the number of prevalent TBI patients with spasticity may be under-estimated; a number of conflicting sources informed this input and the lower estimate was used in the base case analysis;
- relatively low uptake rates for Dysport® was assumed in the financial estimates and utilisation could be higher in clinical practice; and
- the post-stroke population in the requested restriction has expanded relative to the current listing (MAS score of 3 or more), by including patients with a MAS score of 2 or more. These extra patients were not included in the estimates.

6.52 The PSCR and pre-PBAC Response acknowledged the difficulty in obtaining data for the proportion of TBI patients with spasticity and noted that the submission presented sensitivity analyses to account for the uncertainty around this subgroup population.

Financial Management – Risk Sharing Arrangements

6.53 The submission stated that the Sponsor would be willing to enter into a Risk Sharing Arrangement to minimise the risk of leakage into populations where the cost-effectiveness of Dysport® has not been established by the PBAC (e.g. non-acute aetiologies of spasticity of multiple sclerosis and cerebral palsy).

Quality use of medicines

6.54 The ESC acknowledged that sub-optimal targeting of botulinum toxin injections to the affected muscles may occur in clinical practice.

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

7 PBAC Outcome

7.1 The PBAC did not recommend an extension of the current PBS listing for Clostridium botulinum type A toxin-haemagglutinin complex (Dysport®) for treatment of moderate to severe focal spasticity of the upper limb following a stroke, to include spasticity following an acute event other than stroke, on the basis of uncertain clinical benefit, uncertain cost-effectiveness, and high and uncertain financial impact.

7.2 The PBAC acknowledged the input from two health professionals which were supportive of extending the listing for Dysport® and considered the advice received during the sponsor hearing to be informative. The PBAC concluded that there was a clinical need for treatments of upper limb focal spasticity following an acute event.

7.3 The PBAC noted that the TGA, in its decision to grant market authorisation, accepted a favourable benefit to risk ratio for Dysport®, based on spasticity being a common endpoint reached by damage to central motor pathways, and that the underlying aetiology was not particularly important in determining responsiveness to treatment. While the TGA's conclusion may be reasonable for determining a benefit to risk ratio, when determining cost effectiveness and particularly when predicting longer term outcomes such as functional improvements, the PBAC considered that the lack of evidence regarding the effectiveness of Dysport® in treating upper limb focal spasticity due to aetiologies other than stroke created uncertainty. In addition, patients with upper limb spasticity of differing aetiologies were considered likely to have different prospects for rehabilitation and varied goals for treatment; this also affects the assessment of whether it is reasonable to extrapolate benefits to the broader upper limb population, and determination of cost effectiveness.

7.4 The PBAC noted that the key trial, Study 145, consisted of a single injection during a randomised, double-blind phase, followed by up to four treatments in an open label extension, Study 148. The PBAC considered that there was a lack of comparative evidence beyond the first injection, and insufficient evidence to inform the benefit of treatment, particularly beyond the first year of treatment. The PBAC also noted that there was limited data and, accordingly, a high level of uncertainty surrounding the treatment effect, for the treatment of spasticity resulting from events other than

stroke.

7.5 The PBAC considered that the nominated comparator of standard of care/placebo was appropriate.

7.6 The PBAC noted that the primary outcome of the key trial was change in spasticity, measured by the Modified Ashworth Score (MAS). The nominated minimal clinically important difference (MCID) was a reduction in MAS score of at least one, using the 'derived MAS' coding convention, at Week 4. The PBAC noted that the use of the 'derived MAS' coding convention was not consistent with the historical coding convention which was used in the November 2007 submission for Dysport® in the treatment of upper limb spasticity following a stroke or the current PBS listing. 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. The PBAC considered that further clinical input surrounding the use of the historical coding convention and the 'derived MAS' scale in clinical practice would be beneficial.

7.7 The PBAC considered that the benefit of Dysport® compared to placebo in the treatment of focal spasticity of the upper limb following an acute event other than stroke could not be assessed as these patients were poorly represented in the key trial. The PBAC considered that the subgroups of patients with spasticity following a traumatic brain injury were very small and analyses were *post-hoc* and not powered to detect statistical significance. The PBAC noted that no evidence was presented for upper limb spasticity due to other aetiologies such as spinal cord injury, hypoxia or infection.

7.8 The PBAC, noting that the submission did not make a claim regarding the safety of Dysport®, considered that Dysport® was inferior compared to standard of care/placebo.

7.9 The PBAC recalled that it accepted a cost per responder analysis of less than $15,000 when considering Dysport® for the treatment of upper limb focal spasticity following a stroke (November 2007, Dysport® PSD). The PBAC noted that the cost per responder, when response was defined as a MAS improvement of greater than one and re-estimated using the historical MAS coding convention, was considerably higher. The PBAC also noted that as efficacy outcomes were based on Study 145, the estimated cost per responder was driven by response in stroke patients and the applicability of the results to patients with upper limb spasticity following an acute event other than stroke was uncertain.

7.10 The PBAC accepted the mixed approach used to estimate the financial implications of the proposed extension to listing, but agreed with the DUSC that the financial estimates may have been under-estimated given the number of TBI patients were obtained from conflicting data sources and lower estimates were used in the base case analysis. The PBAC considered that the estimated $30 - $60 million additional cost to government over the first six years of extending the current listing was uncertain. Given the uncertainty, the PBAC considered that any future submission for upper limb

focal spasticity following an acute event should consider proposing an utilisation cap.

7.11 The PBAC considered that the uncertainty surrounding the treatment effect of Dysport® in patients with spasticity due to aetiologies other than stroke was unlikely to be substantially reduced by future high quality data and that such high quality data were not likely to become available. These uncertainty issues could be mitigated through adjustment of the requested price to deliver a lower incremental cost-effectiveness ratio.

7.12 The PBAC noted that this submission is not eligible for an Independent Review as it was a request to extend an existing listing.

Outcome:
Rejected

8 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.

9 Sponsor's Comment

Ipsen is committed to working with the PBAC and Department of Health to ensure that patients with spasticity have access to Dysport at the earliest opportunity.