6.02 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 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 limbs following an acute event (e.g. stroke, traumatic brain injury (TBI), hypoxia, infection). This is the first submission with this indication for consideration by the PBAC. Dysport® is currently PBS listed for the treatment of adults with moderate to severe spasticity of the upper limbs following stroke, and a number of other indications.

1.2 At the November 2018 meeting the PBAC also considered a submission for Dysport® use in the upper limb, to extend the PBS listing from following stroke to following an acute event (Item 6.03), and botulinum toxin type A (BOTOX®) for the treatment of focal spasticity of the lower limb following a stroke (Item 7.02).

1.3 The basis for the requested listing was cost-effectiveness of Dysport® plus standard of care compared with standard of care alone. The modelled economic analysis estimated improved quality of life associated with improved walking speed from treatment; however, the trial evidence did not demonstrate a difference in walking speed between the arms.

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

Component	Description
Population	Patients with moderate to severe spasticity of the lower limbs, resulting from an acute event that has occurred two years or less prior to commencing treatment. An acute event is an event that leads to an upper motor neuron lesion resulting in spasticity such as a stroke, traumatic brain injury (TBI), infection or hypoxia.
Intervention	Dysport as adjuvant to standard of care. The dose injected in each lower limb is tailored to the patient but without exceeding the total dose of 1500U, administered no sooner than every 12 weeks. If treatment is required in both upper and lower limbs, the total dose (upper and lower combined) should not exceed 1500U.
Comparator	Standard of care (placebo), including physiotherapy and/or oral spasticity medication.
Outcomes	Change in spasticity Reduction in Modified Ashworth Scale (MAS) score in the PTMG Active functioning Improved speed in 10-meter comfortable barefoot walking test PGA of overall treatment response
Clinical claim	In patients with moderate to severe spasticity of the lower limbs, Dysport is more effective than placebo at improving spasticity (MAS) and active functioning (walking speed), and no worse in terms of safety.

Abbreviations: MAS=modified Ashworth scale; PGA=Physician's Global Assessment; PTMG=primary targeted muscle group; TBI=traumatic brain injury.
Source: Tables 2 and 1.4, pp3 and 22 of the submission.

For more details 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	5	0	$1,515.49	Dysport®	Ipsen Pty Ltd
500 units injection, 1 vial	3	0	$1,618.53	Dysport®	Ipsen Pty Ltd

Category / Program :	Section 100 – Botulinum Toxin Program
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Lower limb spasticity *following an acute event*
PBS Indication: **Treatment phase:**	Moderate to severe spasticity of the lower limb *following an acute event* ~~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 lower limb/s following an acute event, defined as a Modified Ashworth Scale rating of ~~2~~ *3* or more, **AND** ~~The treatment must be initiated between 3 months and 2 years following the acute 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 an improvement in walking speed of 0.13m/s) after four treatment periods *(with any botulinum toxin type A) per lower limb,* **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.* ~~*The maximum total dose per patient is 1500U every 12 weeks.*~~
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.*

[a] Dispensed price calculated during the evaluation using PBAC pricing calculator version 28

[b] The submission quoted DPMQ of $1,515.35 and $1,618.40 respectively for the 300U and 500U injection

Note: Dysport was subject to a 14.5% price reduction as of 1 June 2018 (as Dysport had previously taken a 5% statutory price cut in 2015, and will subsequently take a further 10% and 5% price cut for being listed on the PBS for longer than 15 years). The DPMQ takes into account these statutory price cuts.

Source: Tables 1.11 and 1.12, pp47 and 49 of the submission.

2.2 The Sponsor requested the same price per vial as listed for treatment of spasticity of the upper limbs following stroke. It was not clear why the ex-manufacturer price per unit is higher for the 500U vial ($1.05 per unit) compared with the 300U vial ($0.98 per unit), which resulted in a higher requested DPMQ for the 500U formulation. Higher doses (hence more vials) are required for treatment of lower limbs compared to upper limbs.

2.3 The wording of the requested restriction had some similarities to the current PBS listing of Dysport® for spasticity of the upper limb and incorporated some changes requested by the Rehabilitation Medicine Society of Australia and New Zealand (RMSANZ) in correspondence considered at the July 2018 PBAC meeting designed to facilitate the 'expansion of funded conditions to include muscle overactivity of any aetiology'.

2.4 The key differences between the requested lower limb restriction and the current PBS listed upper limb restriction were:

- Treatment for the upper limb was restricted to patients following stroke. The requested lower limb restriction extended this aetiology to post-acute event, defined by the submission as an event that leads to an upper motor neuron lesion resulting in spasticity such as stroke, TBI, infection, hypoxia. The PBAC recognised that the RMSANZ requested that botulinum toxin be available for lower limb focal spasticity due to aetiologies other than stoke, but noted that there were limited data for these other aetiologies presented in the submission.
- Treatment for the upper limb was restricted to patients with "moderate to severe spasticity defined as a MAS score of 3 or more". The submission proposed "moderate to severe spasticity defined as a MAS score of 2 or more" which aligned with the eligibility criteria of the key trial which included toxin naïve patients with a MAS ≥ 2 and toxin non-naïve patients with a MAS ≥ 3. The PBAC noted that a change in the eligibility criterion for treatment from MAS ≥ 3 to MAS ≥ 2 was not requested by the RMSANZ. The PBAC acknowledged that the key trial (Study 140) enrolled toxin naïve patients with MAS ≥ 2; however, considered that the PBS eligibility criteria should remain consistent with that of the upper limb in defining moderate to severe spasticity as a MAS score of 3 or more. The PBAC noted that the mean baseline MAS score for patients enrolled in Study 140 in the gastrocnemius soleus complex was 3.8.

- The proposed restriction requested initiation "between 3 months and 2 years post-acute event". Although noting a lack of evidence for the optimal timing of the initiation of treatment, the PBAC recommended removing the criteria, determining that the timing of the onset of treatment should be at the discretion of the physician. This was supported by the RMSANZ.
- Treatment for the upper limb is currently limited to a maximum of four treatment cycles (any brand of botulinum toxin) per upper limb per lifetime (given that response criteria was met). No lifetime treatment limit was proposed in the requested lower limb listing. The PBAC agreed that the removal of a lifetime limit of four treatments was consistent with clinical practice for continuing responders and consistent with the recommendation by the RMSANZ. 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.
- The submission defined treatment response as an improvement in walking speed of at least 0.13 m/s after four treatment cycles. The PSCR stated that the 10 m comfortable barefoot walking test, which aligned with the test used in the key clinical trial, was the most appropriate for assessing walking speed. The evaluation considered that walking speed may not be a reasonable proxy for community ambulation, which is determined by other factors (such as balance, motor function, endurance and assistive walking aids), or for meaningful changes to patient functioning and quality of life. The RMSANZ stated that intended outcomes of treatment with botulinum toxin included reduced impairment (i.e. spasticity, pain), improved activity and participation (i.e. independent living and mobility), improved passive function (i.e. personal hygiene), improved quality of life and reduced carer burden. The PSCR claimed that the British National Guidelines for the treatment of spasticity recommend the use of a 10 m walking speed test as part of patients on-going monitoring, specifically where improvements in their mobility have been identified as a goal for treatment. The ESC considered that while 10 m walking speed test is a commonly used outcome measure, it may not correlate to a patient-relevant outcome measure and does not adequately capture activities of daily living. The PBAC noted the use of the 10 m walking speed test was commonly used in the assessment of patients with lower limb spasticity. However, the PBAC agreed with the ESC that walking speed may not adequately capture improvements to overall patient functioning or quality of life. The PBAC also expressed concern that the clinical relevance of walking speed improvements may vary with aetiology, age and baseline walking speeds, and may be difficult to test in some patients. The PBAC noted that as MAS was the primary outcome for Study 140 and was used as the continuation criteria for upper limb spasticity that a continuation criterion based on MAS might be more reasonable.

2.5 Some patients may require treatment for spasticity in both the upper and lower limbs concurrently (as was the case for up to 48% of the population in the open label extension, Study 142). The approved Australian Product Information recommends the same maximum dose per person, as for lower limbs alone (1,500U at an interval of at least 12 weeks).

For more details 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 lower limbs in adults".

3.2 The PBAC noted that the TGA approved Dysport® for the treatment of focal spasticity of the lower 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 children, focal spasticity of the upper limbs, spasmodic torticollis, blepharospasm, hemifacial spasm and glabellar lines.

Previous PBAC considerations

3.4 Dysport® has not been considered for lower limb spasticity previously. It was approved for the treatment of upper limb focal spasticity following stroke in November 2007.

3.5 In May 2018, DUSC provided advice to the PBAC in a review of utilisation of botulinum toxin type A (BoNT-A) supplied through the PBS for treatment of spasticity in patients with cerebral palsy (CP) or following a stroke, and for spasmodic torticollis, blepharospasm and hemifacial spasm. This followed a 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. Both the DUSC report and the RMSANZ requests were considered by the PBAC in July 2018.

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

4 Population and disease

4.1 Spasticity of the lower limbs (in 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 The dose administered, which is given by intramuscular injection, is 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 not more frequently than every 12 weeks. 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.

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

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

5 Comparator

5.1 Standard of care (placebo). The ESC considered standard of care (placebo) to be a reasonable comparator, noting that given the PBAC will also consider an application to list BOTOX® on the PBS for spasticity of the lower limb at the November 2018 meeting, BOTOX® would be a relevant near market comparator.

For more details 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 discussed the use of Dysport® in clinical practice, and stated that the primary goal of treatment is to improve patient safety, and then to improve function and patient goals. The clinician described the action of Dysport® as providing a window to permit stretching and training of antagonist muscles. In response to the Committee's questions, the clinician stated that, while patients with spasticity following stroke or TBI were easier to recruit into trials, spasticity from other causes manifests similarly. The clinician stated that the goal setting for patients may differ across aetiologies, and the injections are targeted according to patients' goals.

Consumer comments

6.2 The PBAC noted and welcomed the input from four health professionals via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with Clostridium botulinum toxin including improving mobility, improving quality of life, reducing pain and the burden of care for carers and family.

Clinical trials

6.3 The submission was based on one head-to-head randomised trial comparing Dysport® to placebo (Study 140) and its associated open label extension (Study 142).

6.4 The submission identified five supportive randomised controlled trials (and one open label extension) which were considered less applicable to the proposed listing than the main trial (Study 140) due to differences in the reported outcomes, data analysis and/or administration of lower doses of Dysport®. Evidence reported in the supportive trials was not relied on for the clinical claim nor used in the modelled economic evaluation.

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

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Main trial		
Study 140	Clinical study report (CSR) - A Phase III, Multicentre, Double Blind, Prospective, Randomised, Placebo Controlled Study, 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 Study 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, Banach M, Kocer S, Jech R, Khatkova S, Benetin J, Vecchio M, McAllister P, Ilkowski J, Ochudlo S, Catus F, Grandoulier AS, Vilain C, Picaut P, On behalf of the International AbobotulinumtoxinA Adult Lower Limb Spasticity Study Group, 2017; "Efficacy and safety of abobotulinumtoxinA in spastic lower limb, Randomised trial and extension".	Neurology, 2017; 86:2245-2253
Supportive trials		
Study 700	Clinical study report (CSR) – A Phase III Prospective, multicentre, randomised, double-blind, placebo controlled study to assess the efficacy and safety of 1500 units of Dysport Intramuscular injection in spastic equinovarus deformity of the foot in post-stroke patients.	CSR Report 700, 2004
Study 004 (extension study)	Clinical study report (CSR) – A Phase III prospective, multicentre, open label study to assess the safety and efficacy of repeat treatment of between 500 units and 1500 units of Dysport intramuscular injection in spastic equinovarus deformity of the foot in post-stroke patients.	CSR Study 004, 2015
Study 002	Clinical study report (CSR) – Study on the efficacy and safety of botulinum toxin type A (Dysport), combined with rehabilitation treatment, in patients with post-stroke spasticity of the lower extremity causing club foot. A multicentre, Phase III, randomised, double-blind parallel-group, placebo-controlled study.	CSR Study 002, 2006
Johnson et al 2004	Johnson CA, Burridge JH, Strike PW, Wood DE, Swain ID, 2004; "The Effect of Combined Use of Botulinum Toxin Type A and Functional Electric Stimulation in the Treatment of Spastic Drop Foot After Stroke: A Preliminary Investigation.	Arch Phys Med Rehabil, 2004; 85:902-909
Study 044	Clinical study report (CSR) – A multicentre, double-blind, prospective, randomised, placebo- controlled, dose-ranging study to compare the efficacy and safety of three doses of Dysport with placebo in spastic equinovarus deformity of the foot in post-stroke patients.	CSR Study 044, 2000
	Pittock SJ, Moore AP, Hardiman O, Ehler E, Kovac M, Bojakowski J, al Khawaja I, Brozman M, Kanovsky P, Skorometz A, Slawek J, Reichel G, Stenner A, Timerbaeva S, Stelmasiak Z, Zifko UA, Bhakta B, Coxon E on behalf of the trial participants; "A double-blind randomised placebo-controlled evaluation of three doses of botulinum toxin type A (Dysport®) in the treatment of spastic equinovarus deformity after stroke.	Cerebrovasc Dic, 2003; 15:289-300
Burbaud et al 1996	Burbaud P, Wiart L, Dubos LJ, Gaujard E, Debelleix X, Joseph PA, Mazaux JM, Bioulac B, Barat M, Lagueny A 1996; "A randomised, double-blind, placebo controlled trial of botulinum toxin in the treatment of spastic foot in hemiparetic patients";	Journal of Neurology, Neurosurgery and Psychiatry, 1996; 61:265-269

Source: Table 2.3, p55 of the submission.

6.6 The key features of the main trial are summarised in Table 3. A description of the supportive trials was not presented given data were not relied on by the submission.

Table 3: Key features of the included evidence

Trial	N	Design/duration	Bias	Patient population	Key outcomes	Use in model
Study 140	388	R, DB, MC, PC 12 to 24 weeks	Low	Post-stroke or TBI prior ≥ 6 months; hemiparesis; LL spasticity; MAS ≥ 2 if toxin naïve, MAS ≥ 3 if toxin non-naïve; comfortable barefoot WS 0.1-0.8 m/s; ± physiotherapy ± anti-spasticity drugs	ΔMAS, PGA, ΔCB walking speed, EQ-5D.	<u>Subgroup:</u> Acute event ≤ 2 years. <u>Outcome:</u> ΔCB walking speed *(≈QoL)*
Study 142 (extension study)	345^	OL, MC 6 to 18 months (4 treatment cycles‡ of 12 to 24 weeks)	High	Completion of Study 140 without protocol violation and/or AEs.		

Abbreviations: Δ=change in; AE=adverse event; BL=baseline phase; CB=comfortable barefoot; DB=double blind; LL=lower limb; MAS=modified Ashworth Scale; MC=multicentre; OL=open label; PC=placebo controlled; PGA=physician's global assessment; QoL=quality of life; R=randomised; TBI=traumatic brain injury; WS=walking speed

^ Previously from Study 140

‡ The study allowed patients with co-existing upper limb spasticity to receive injections of Dysport® 500U into the affected upper limbs (in addition to 1000U in the lower limb) in Cycles 3 and 4.

Source: Table 2.4, pp60-61 of the submission.

6.7 Study 140 was a multi-centre (53 sites in 11 countries including Australia), double-blind, randomised, placebo-controlled trial, which assessed the efficacy and safety of a single treatment cycle of Dysport® at two different doses (1000U and 1500U) versus placebo (saline) in adults with spasticity of the lower limbs following stroke (approximately 87% of patients) or TBI (approximately 13% of patients). The PBAC noted that spasticity due to other aetiologies (e.g. spinal cord injury or hypoxia) was not represented in the trial.

6.8 No physiotherapy or muscle relaxants were initiated within four weeks of randomisation or during the double-blind phase. Patients who initiated physiotherapy or muscle relaxants, at least four weeks prior to randomisation, continued at the same frequency and intensity up to Week 4 and, whenever possible, until the end of the trial. Approximately 60% of patients enrolled in Study 140 received concomitant physiotherapy. Study 140 did not report whether patients received other concomitant physical therapies recommended in the guidelines (including postural management, casting and splinting and occupational therapy). The submission appeared to use the terms "physical therapy" and "physiotherapy" interchangeably. Given the submission did not present data to inform the proportional use of physical therapy, including physiotherapy, in the Australian setting, it was unclear whether the trial population was wholly representative of patients who would receive botulinum toxin on the PBS.

6.9 Patients who completed Study 140 without protocol violation and/or adverse events entered the extension study, Study 142, and received open label Dysport® 1500U (or 1000U if patients experienced previous events which posed an unacceptable risk) for a maximum of four additional treatment cycles, at minimum 12 weeks intervals, over 18 months. In Cycles 3 and 4, concomitant treatment of affected upper limb muscles (maximum 500U) was allowed, within the total dose of 1500U.

Comparative effectiveness

6.10 The submission's clinical claim was based on change in spasticity (measured by change in MAS score in the gastrocnemius-soleus complex, GSC), change in walking speed (measured by the 10 m comfortable barefoot walking test) and treatment response criteria (measured by Physician Global Assessment, PGA).

6.11 The MAS (see Table 4) is a common outcome reported in trials of botulinum toxins 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 is a subjective functional outcome, which is an investigator rated response to treatment after injection of treatment.

Table 4: 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: Section 2.4.3.1, p76 of the submission and compiled during evaluation

6.12 The historical coding convention for the MAS was used in this submission. The proposed PBS listing for lower limb spasticity is based on the historical coding convention. The ESC questioned whether the historical or the more recent 'derived MAS' coding convention was most commonly used in clinical practice and the implications of this for the requested restriction.

6.13 The submission nominated a reduction of at least one point (MAS ≥ 1) at Week 4 to 6 to be the minimal clinically important difference (MCID). The PBAC had previously considered the outcome of a decrease in MAS of at least one point, in at least one joint, at Week 20 to be clinically significant when MAS was supported by improvements in Goal Attainment Scale (GAS) and Global Assessment of Benefit (GAB) scores (November 2007, Dysport® PSD). In an earlier determination for BOTOX®, the PBAC had considered a more stringent change from baseline of MAS ≥2 to be meaningful as that was associated with improvement in limb function and hygiene on the Disability Assessment Scale (DAS) (July 2006, BOTOX® PSD). The PBAC considered that a ≥ 1 point improvement in MAS, when accompanied by other functional outcomes such as goal attainment, would likely represent a clinically meaningful response.

6.14 The submission nominated the MCID in walking speed (comfortable barefoot, 10 m) for the PBS population to be an improvement from baseline of at least 0.13 m/s. This

was based on studies by Van Loo et al 2008, Bohannon et al 2013 and Middleton et al 2015. The validity of the nominated MCID was unclear given the studies used a variety of walking speed tests over different durations of rehabilitation. Bohannon et al 2013 stated that it may be more useful if the MCIDs were determined for specific periods (e.g. acute, subacute, chronic) given the natural course of recovery after stroke. The PSCR conceded that the type of test used to estimate walking speed did vary between studies, but argued that the tests have been reported to have high reliability (Schivoletto et al 2011), and that the MCID nominated was the second highest from a literature review, with the highest being a MCID of 0.18 m/s in patients with chronic stroke. The ESC considered that the relevance of the walking test in determining change in overall patient functionality was uncertain.

6.15 Table 5 presents the key efficacy outcomes reported in Study 140 (ITT).

Table 5: Key efficacy outcomes reported in Study 140 (ITT)

	Placebo	Dysport 1000U	Dysport 1500U	Dysport vs placebo	
	N=128	N=125	N=128	1000U	1500U
Change in MAS in the GSC (knee extended) from baseline					
LS mean change (95% CI)[a], Wk 4	-0.5 (-0.7,-0.4)	-0.6 (-0.8,-0.5)	-0.8 (-0.9,-0.7)	-0.1 (-0.3, 0.1), p=0.2859	**-0.3 (-0.5,-0.1), p=0.0091**
LS mean change (95% CI) [a], Wk12	-0.4 (-0.5,-0.2)	-0.4 (-0.5,-0.2)	-0.6 (-0.7,-0.4)	0.0 (-0.2,0.2), p=0.9536	**-0.2 (-0.4,0.0), p=0.0324**
MAS responder (≥1 grade reduction in MAS in the GSC, knee extended)					
Responder n (%)[b], Wk4	47 (36.7%)	53 (42.4%)	60 (46.9%)	p=0.2228	p=0.0527
Responder n (%)[b], Wk12	36 (28.1%)	33 (26.4%)	42 (32.8%)	p=0.9761	p=0.2459
PGA score					
n	n=128	n=124	n=125	-	
LS mean (95% CI)[a], Wk4	0.7 (0.5, 0.9)	0.9 (0.7, 1.1)	0.9 (0.7, 1.1)	0.3 (0.0, 0.5), p=0.0640	0.3 (0.0, 0.5), p=0.0665
LS mean[c], ranked values back transformed to original scale, Wk4	0.6 (NR)	0.8 (NR)	0.8 (NR)	**p=0.0466**	**p=0.0406**
PGA responders (score ≥+1)					
Responders n (%)[b], Wk4	63 (49.2%)	73 (58.4%)	76 (59.4%)	p=0.0851	**p=0.0237**
Change in comfortable 10 m barefoot walking speed (m/s)					
LS mean change (95% CI)[a], Wk4	0.05 (0.03,0.07)	0.05 (0.03,0.07)	0.04 (0.03,0.06)	0.01 (0.02, 0.03) p=0.7247	-0.01 (-0.03,0.02) p=0.7266
n	n=120	n=120	n=120	-	
LS mean change (95% CI)[a], Wk12	0.05 (0.03,0.07)	0.07 (0.05,0.09)	0.06 (0.04,0.07)	0.02 (-0.01, 0.05) p=0.2056	0.0 (-0.02, 0.03) p=0.7612

Abbreviations: BoNT=botulinum toxin; CI=confidence interval; GSC=Gastrocnemius soleus complex; ITT=intention to treat; LS mean=least square mean; N=total patients in group; MAS=modified Ashworth Scale; PGA=physician global assessment; wk=week

[a] ANCOVA, controlling for the randomisation stratification factor (BoNT treatment status at baseline) and the centre, all as fixed effects.

[b] Logistic regression, controlling for the randomisation stratification factor (BoNT treatment status at baseline) and the centre, all as fixed effects.

[c] ANCOVA based on ranked values, controlling for the randomisation stratification factor (BoNT treatment status at baseline) and the centre as explanatory variables.

Source: Section 2.5.1.3 pp85-86 of the submission; Tables 2.15 and 2.19, pp83 and 93 of the submission; Tables 17, 18, 21 and 25, pp58-63 and p67 of CSR Study 140.

6.16 The results demonstrated:

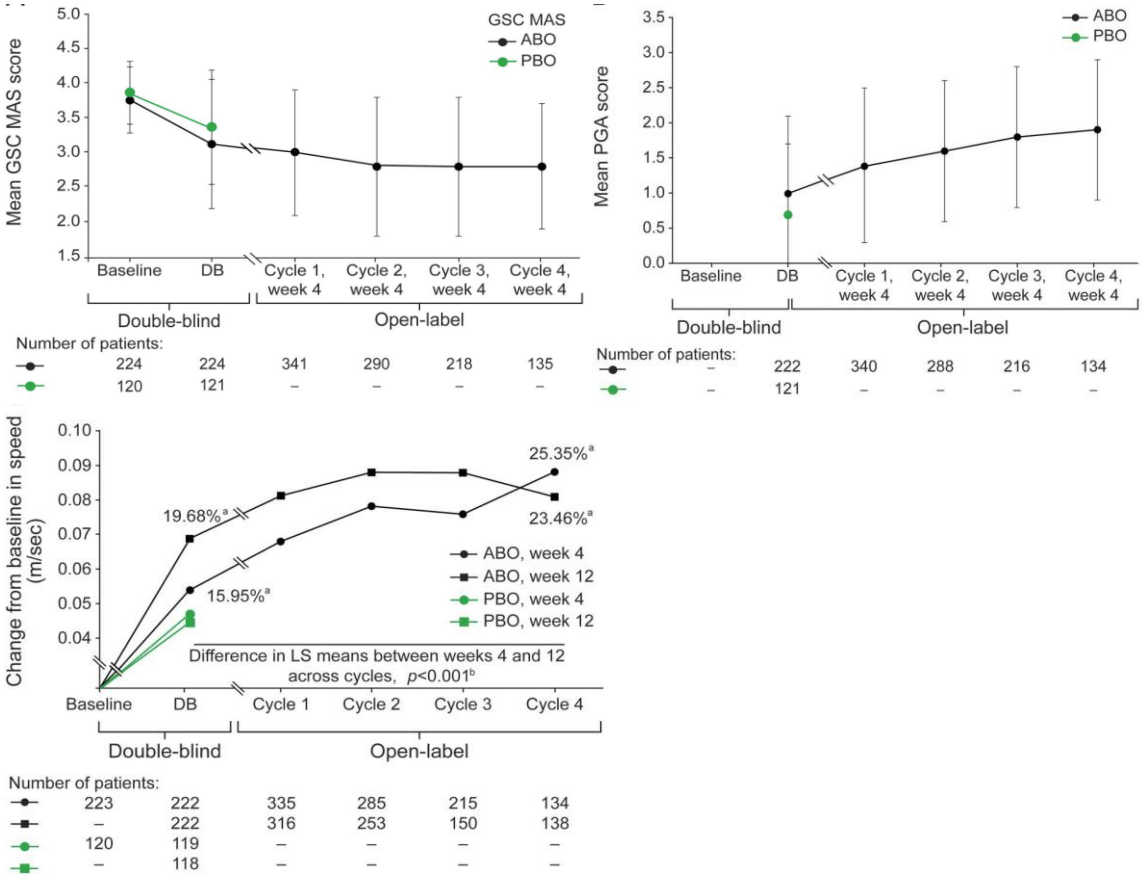
- The reduction in MAS score was statistically significantly greater for Dysport® 1500U compared to placebo at both Week 4 (-0.03, p=0.0091) and Week 12 (-0.2,

p=0.0324). There was no difference between Dysport® 1000U and placebo at either time point.

- The proportion of MAS responders was numerically higher for Dysport® 1500U compared to placebo at both Week 4 (46.9% versus 36.7%, p=0.0527) and Week 12 (32.8% versus 28.1%, p=0.2459); however, the differences were not statistically significant. There was no difference between Dysport® 1000U and placebo at either time point.
- The average PGA score was numerically higher for Dysport® 1000U (+0.3, p=0.0640) and 1500U (+0.3, p=0.0665) compared to placebo at Week 4; however, the differences were not statistically significant in the pre-specified analysis. An exploratory *post-hoc* analysis on ranked PGA score reported a significant improvement for both doses of Dysport® compared to placebo. The TGA clinical evaluator questioned the validity of the *post-hoc* analysis.
- There were significantly more PGA responders on Dysport® 1500U compared to placebo at Week 4 (p=0.0237), although the difference in response rate was only 10.2%.
- There was no improvement in comfortable 10 m barefoot walking speed for either dose of Dysport® compared to placebo.

6.17 Figure 1 presents the mean MAS scores, mean PGA scores and mean change in walking speed reported in the open-label extension Study 142 from baseline (Study 140), for combined Dysport® 1500U and 1000U doses.

Figure 1: Mean MAS score in the GSC (knee extended), mean PGA score and mean change in comfortable 10m barefoot walking speed in the open label extension Study 142 from baseline (Study 140), for combined Dysport 1500U and 1000U



Abbreviations: ABO=Abobotulinumtoxin A (Dysport); DB=double-blind study; LS=least-squared; PBO=placebo.
Baseline refers to baseline of double-blind study, prior to first injection. Error bars show SD.
[a] Percentage improvement from baseline.
[b] A *post-hoc* analysis compared change from baseline in 10m walking speed at Week 4 vs Week 12 across cycles using a model for repeated measures; greater improvement was observed at Week 12 compared with Week 4 across cycles.
Source: Figure 2.8, p92, Figure 2.9, p94 and Figure 10, p97 of the submission.

6.18 The results from the open label extension, Study 142, indicated an improvement in mean MAS score, mean PGA score and change in walking speed compared to baseline (Study 140) over time. It should be noted that 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.

6.19 Efficacy data from the supportive trials was inconsistent. For example, two trials (Study 044, Burbaud et al 1996) demonstrated a significant improvement in MAS associated with Dysport®, whereas three trials (Study 700, Study 002, Johnson et al 2004) reported no difference in proportion of MAS responders (≥ 1 grade), proportion with any improvement in MAS, or median MAS compared with placebo/control. Although one trial (Johnson et al 2004) demonstrated a significant improvement in walking speed (10 m walk test), four trials (Study 044, Study 700, Study 002 and

Burbaud et al 1996) reported no difference in walking speed (10 m walk test), walking distance (2 minute walk test) or walking speed response (≥ 10% improvement from baseline in time taken to walk 10 m).

6.20 A *post-hoc* analysis of change in walking speed from baseline (Study 140) in the open-label extension Study 142, by time since acute event at randomisation, indicated a larger absolute change in walking speed over time for the subgroup ≤ 2 years post-acute event. While the mean change in walking speed appeared to be higher for patients with more recent events, a much higher proportion of patients in the subgroup ≤ 2 years post-event had walking speeds < 0.4m/s, were treatment-naïve, and were younger at baseline compared to the ITT population. Hence, patients with more recent events may have more opportunity to demonstrate a larger change in walking speed over time compared to patients who have already improved from previous treatments.

6.21 A *post-hoc* analysis of walking speed responder (*post-hoc* outcome, defined as ≥ 0.13m/s improvement in walking speed from baseline in Study 140) in the open-label extension Study 142 demonstrated patients initially treated with placebo (standard of care alone) experienced a lagged response.

6.22 For the modelled economic analysis, the submission proposed that the *post-hoc* subgroup ≤ 2 years post-acute event in Study 140 was more applicable to the PBS population than the ITT population. The submission inappropriately did not provide any pharmacological, biological or clinical rationale for restricting access to patients within the nominated *post-hoc* trial subgroup. The PSCR argued that the biological rationale for the subgroup analyses is that once spasticity is established, the chronically shortened muscle may develop physical changes that lead to deformities, impairing capacity for activities required in daily life. The PSCR claimed that in patients with these characteristics the intent of treatment might be most appropriately focused on improving passive functioning rather than active functioning such as walking speed, and the *post-hoc* subgroup is representative of a patient population who have the muscle plasticity to potentially obtain active functional improvements.

6.23 The submission inappropriately did not present the relative or absolute treatment effects for any pre-specified outcomes in the double blind Study 140 for the nominated subgroup or its complement. The PSCR provided additional data for the subgroup ≤ 2 years post-event and its complement (> 2 years) across some pre-specified outcomes (see Table 6). The PSCR argued that the main findings from these analyses supported the rationale that outcomes in the ≤ 2 years subgroup were superior to the outcomes in the complementary sub-population. No formal comparison of the subgroups was provided. The ESC considered that the superiority of outcomes in the ≤ 2 years post-event subgroup compared with the > 2 years subgroup was not apparent from data provided in the PSCR. The ESC noted that none of the outcomes (mean change in MAS from baseline, MAS responder, mean change in walking speed or walking speed responder) were statistically different to placebo in either of the subgroups at the 4 week or 12 week time points.

Table 6: Key efficacy outcomes reported in Study 140 (≤2 years and >2 years since onset)

	≤2 years			>2 years		
	Placebo	Dysport 1500U	Dysport vs Placebo	Placebo	Dysport 1500U	Dysport vs Placebo
	N=43	N=44		N=85	N=84	
Change in MAS in the GSC (knee extended) from baseline						
LS mean change (95% CI), Wk 4	[redacted]					
LS mean change (95% CI), Wk12	[redacted]					
MAS responder (≥1 grade reduction in MAS in the GSC, knee extended)						
Responder n (%), Wk4	[redacted]					
Responder n (%), Wk12	[redacted]					
PGA responders (score ≥+1)						
Responders n (%), Wk4	[redacted]					
Change in comfortable 10 m barefoot walking speed (m/s) from baseline						
	N=38	N=43	-	N=85	N=84	-
LS mean change (95% CI), Wk4	[redacted]					
LS mean change (95% CI), Wk12	[redacted]					
Walking speed responder (≥0.13 m/s improvement)						
Responder n (%), Wk4	[redacted]					
Responder n (%), Wk12	[redacted]					

Abbreviations: BoNT=botulinum toxin; CI=confidence interval; GSC=Gastrocnemius soleus complex; ITT=intention to treat; LS mean=least square mean; N=total patients in group; MAS=modified Ashworth Scale; PGA=physician global assessment; wk=week
Source: Dysport® PSCR

6.24 The *post-hoc* analyses in the open-label extension study could not demonstrate that Dysport® was more effective compared to placebo in patients receiving treatment ≤ 2 years post-event as all patients in the open label phase received active treatment.

Comparative harms

6.25 Table 7 summarises the adverse events reported in Study 140. A significantly higher proportion of patients on Dysport® (both 1000U and 1500U doses) compared to placebo experienced at least one treatment emergent adverse event. The proportion of patients experiencing adverse events was generally similar between the two Dysport® doses.

6.26 The most common adverse events for Dysport® listed in the Product Information included spread of effects of the toxin to sites remote from the injection site, muscle weakness, aspiration and falls. There were also injection related reactions, which included localised infection, pain, inflammation, paraesthesia, hypesthesia, tenderness, swelling, erythema and/or bleeding/bruising.

Table 7: Summary of key adverse events in the trials

Adverse event, n (%)	Placebo	Dysport 1500U	Total Dysport	Total Dysport vs placebo	
	N=130	N=128	N=255	RD (95% CI)	RR (95% CI)
At least one AE	41 (31.5%)	54 (42.2%)	111 (43.5%)	**0.12 (0.02, 0.22)**	**1.38 (1.03, 1.84)**
At least one TEAE	41 (31.5%)	52 (40.6%)	107 (42.0%)	**0.10 (0.00, 0.20)**	1.33 (0.99, 1.78)
Any TEAE of Special Interest	7 (5.4%)	13 (10.2%)	19 (7.5%)	0.02 (-0.03, 0.07)	1.38 (0.60, 3.21)
Remote spread effects	6 (4.7%)	12 (9.4%)	18 (7.1%)	0.02 (-0.02, 0.07)	1.53 (0.62, 3.76)
Muscular weakness	4 (3.1%)	8 (6.3%)	11 (4.3%)	0.01 (-0.03, 0.05)	1.40 (0.46, 4.32)
Dysphagia	1 (0.8%)	1 (0.8%)	3 (1.2%)	0.00 (-0.02, 0.02)	1.53 (0.16, 14.6)
Hypersensitivity	1 (0.8%)	1 (0.8%)	1 (0.4%)	-0.00 (-0.02, 0.01)	0.51 (0.03, 8.09)
Multiple allergies	0	1 (0.8%)	1 (0.4%)	0.00 (-0.00, 0.01)	2.51 (0.06, 100.9)
Rash	1 (0.8%)	0	0	-0.01 (-0.02, 0.01)	0.25 (0.01, 4.76)

Abbreviations: AE=adverse event; CI=confidence interval; n=number of patients reporting data; N=total patients in group; RD=risk difference; RR=relative risk; TEAE=treatment emergent adverse event;
Note: patients may be recorded in more than one category. TEAEs of special interest were sorted by descending frequency of system organ class and descending frequency of preferred term within the organ class for Dysport 1500U.
Source: Tables 2.26 and 2.27, pp103-104 of the submission and Table 50, p102 and Table 53, p106 of CSR Study 140.

Benefits/harms

6.27 A summary of the comparative benefits and harms for Dysport® 1500U versus placebo is presented in Table 8.

Table 8: Summary of comparative benefits and harms for Dysport 1500U and placebo from Study 140 (ITT)

Benefits						
Study 140	**Dysport 1500U n/N**	**Placebo n/N**	**RR (95% CI)**	**Event rate/100 patients**		**RD (95% CI)**
				Dysport 1500U	**Placebo**	
MAS responder (≥1 grade reduction in MAS in the GSC, knee extended)						
Week 4	60/128	47/128	NS#	46.9	36.7	NS#
Week 12	42/128	36/128	NS#	32.8	28.1	NS#
Harms						
≥ 1 AE	54/128	41/130	**1.34 (0.97, 1.85)**	42.2	31.5	**0.11 (-0.01, 0.22)**
≥ 1 TEAE	52/128	41/130	1.29 (0.93, 1.79)	40.6	31.5	0.09 (-0.03, 0.21)

Abbreviation: AE=adverse event; BoNT=botulinum toxin; CI=confidence interval; GSC=Gastrocnemius soleus complex; MAS=modified Ashworth scale; RD=risk difference; RR=risk ratio; TEAE=treatment emergent adverse event;
The pre-specified analysis, logistic regression controlled for prior BoNT experience at baseline and the centre (all as fixed effects), reported no statistically significant differences.
Source: Tables 2.15, p83 and Table 2.25, p102 of the submission and Table 21, p63 and Table 49, p101 of CSR Study 140.

6.28 On the basis of direct evidence presented by the submission, for every 100 patients treated with Dysport® 1500U versus placebo:

- There was no difference in the proportion of MAS responders at Week 4 and 12, once adjusted for baseline.
- Approximately 11 more patients would experience an AE.

Clinical claim

6.29 The submission described Dysport® (as adjuvant to standard of care) as superior in terms of comparative effectiveness (spasticity, active functioning and subjective treatment response) and non-inferior in terms of comparative safety compared to standard of care alone (placebo).

6.30 The claim of superior effectiveness compared to standard of care was not supported by ESC as:

- There was minimal evidence to support the effectiveness of Dysport® in the treatment of focal spasticity due to acute events other than stroke.
- Although the mean reductions in the MAS score at Week 4 and 12 were statistically significant for Dysport® 1500U compared to placebo, the differences were not clinically significant given they did not meet the submission's nominated MCID of ≥ 1 point reduction in the MAS score. The proportion of MAS responders (defined as ≥ 1 point reduction in MAS) was not significantly different between the Dysport® and placebo patients (p=0.0527 at Week 4, p=0.2459 at Week 12).
- Although there were significant improvements in ranked PGA score at Week 4 for Dysport® 1500U and 1000U compared to placebo in an exploratory *post-hoc* analysis, there were no significant differences between mean PGA scores in the pre-specified analysis (p=0.0640 and p=0.0665, respectively).
- There were no significant differences in change in walking speed (any test, comfortable or maximal, barefoot or with shoes) at Week 4 or Week 12 for either dose of Dysport® compared to placebo; hence, the outcome did not reach the nominated MCID ≥ 0.13 m/s.
- The PSCR presented additional evidence of comparative effectiveness from Study 140 for the subgroup of patient's ≤ 2 years post-event and its complement (> 2 years) across some pre-specified outcomes, which were consistent with the population in the requested restriction. Despite representing a population that the PSCR contended had a greater capacity to respond to Dysport®, there were no statistically significant differences for mean change in MAS, MAS responders, mean change in walking speed or walking speed responders between the Dysport® and placebo arms at Weeks 4 or 12.

6.31 The Pre-PBAC Response stated that the clinical claim of superiority of Dysport® over placebo was based on the change in MAS score in the gastrocnemius-soleus complex and outcomes for PGA score at Week 4, not on walking speed.

6.32 In considering the comparative evidence following the first injection cycle, the PBAC considered that Dysport® treatment, at a dose of 1500U, was not superior to placebo. Although treatment resulted in a small improvement in MAS from baseline at Weeks 4 and 12 compared to placebo, which was statistically significant, the improvement was not clinically significant as it did not exceed the predefined minimal clinically important difference (MCID) of at least a one point reduction in MAS score; and

6.33 The PBAC considered that Dysport®, at a dose of 1000U, was not superior to placebo in terms of effectiveness.

6.34 With respect to safety, the PBAC considered that the submissions claim of non-inferiority compared to standard of care alone was not appropriate as the comparison would be, in practice, between an injection and no injection. In addition significantly

more patients treated with Dysport® experienced at least one AE versus placebo injection.

Economic analysis

6.35 The submission presented a cost-utility analysis based on patients enrolled in Study 140, summarised in Table 9. The submission assumed that walking speed alone (measured by the 10 m comfortable barefoot walk test) was a reasonable surrogate for meaningful change to patient functioning and quality of life. The ESC considered the link between walking speed and patient functioning was not adequately justified in the submission, and poorly supported in the literature. In addition to concerns that walking speed was not a suitable proxy for overall patient functioning, there were no significant differences in change in walking speed (any test, comfortable or maximal, barefoot or with shoes) at Week 4 or Week 12 for either dose of Dysport® compared to placebo in the trial evidence. Hence, the ESC considered that the fundamental justification for conducting a cost-utility analysis based on walking speed alone was not valid.

6.36 The PSCR argued that:

- In the literature, changes in walking speed were assessed as an indicator of function and prognosis following stroke, with the same definitions for health states used as applied in the submitted economic model;
- Australian utilities estimated using EQ-5D-5L instrument demonstrated that there were statistically significant differences between the quality of life in patients across the proposed health states; and
- In the absence of more robust clinical trial data for estimating changes in walking speed, the walking speed responder analyses from Study 142 demonstrated that patients initiated on Dysport® experienced clinically meaningful gains in walking speed after two to three treatment cycles, whilst those who initiated on placebo but subsequently received active treatment in the open label extension, achieved a similar response rate which lagged the Dysport® arm by one treatment cycle. The ESC noted that the number of patients in Study 142 decreased significantly from Cycle 1 (N = 335/316) to Cycle 4 (N = 134/138), suggesting that those who continued were responders only.

6.37 The PBAC agreed with the ESC that the premise for the model was flawed as it was based on a *post hoc* subgroup analysis of a secondary outcome, which was not statistically different from placebo.

Table 9: Summary of model structure

Component	Summary
Population	Study 140 *post-hoc* subgroup ≤ 2 years post-acute event (base case).
Time horizon	10 years in the model base case versus 12 to 24 weeks in the double-blind phase (Study 140) and 53.9 weeks including the open-label extension phase (Study 142).
Outcomes	QALYs
Methods used to generate results	Markov model, cohort expected value analysis.
Health states	Defined by absolute walking speed: • HS1: Household Walker (< 0.4 m/s) • HS2: Limited Community Ambulator (≥ 0.4 m/s to < 0.8 m/s) • HS3: Community Ambulator (≥ 0.8 m/s)
Cycle length	28 days
Transition probabilities	• Transition between health states was estimated from two ordered logit models (change in walking speed category, up or down) from IPD from Study 140 and 142. • Assumed no change in health state after discontinuation of Dysport. • Discontinuation of Dysport due to AEs and failed response criteria estimated from IPD in Study 140 and 142.
Utility values	Estimated from IPD in Study 140 and 142 (random effects model). • HS1, Household Walker (< 0.4 m/s) = 0.4049 • HS2, Limited Community Ambulator (≥ 0.4 m/s to < 0.8 m/s) = 0.4918 • HS3, Community Ambulator (≥ 0.8 m/s) = 0.5400
Costs	Drug and administration costs only

Abbreviation: AE=adverse event; HS=health state; IPD=individual patient data; QALY=quality adjusted life year
Source: Table 3.1, p123 of the submission.

6.38 All patients commenced in one of three walking speed health states (informed by baseline distribution in Study 140): "Household walker (< 0.4 m/s)" (HS1), "Limited community ambulator (≥ 0.4 m/s to < 0.8 m/s)" (HS2) and "Community ambulator (≥ 0.8 m/s)" (HS3). In the Dysport® arm, all patients start on treatment and could transition between the health states while remaining on treatment. After treatment discontinuation (due to adverse events or lack of response), patients remained in the same health state for the remainder of the 10-year time horizon. In the placebo arm, patients could transition between the health states indefinitely.

6.39 To estimate transition probabilities between health states, the submission estimated ordered logit regressions to predict 'change' in walking speed (up or down) based on individual patient data (IPD). Patients in the trial were classified by model health states, and the change in walking speed category over study visits (every 28 days) was calculated as either no change (0), a movement up or down one health state (+1 and -1, respectively), or a movement up or down two health states (+2 and -2, respectively). The submission's approach for estimating 'change' in walking speed was difficult to interpret and, despite inclusion of a log transformed time variable, was likely to exaggerate early trends in the trial data over time in the model.

6.40 There were a number of discrepancies in the baseline characteristics between the model and trial populations. The model overestimated the proportion of standard of care patients in the worst health state, HS1, and overestimated the number of Dysport® patients in best health state, HS3. In the Dysport® arm 22% of patients at

baseline were in the HS3 state compared to 2.3% of patients in the standard of care arm. The PSCR conceded that the baseline distributions favoured Dysport® and presented new cost-effectiveness estimates using the baseline distributions from Study 140 and Study 142- see Table 13. The pre-PBAC response acknowledged that errors occurred in the extraction of trial data and presented corrected distributions (Table 10); however, no updated cost-effectiveness results were presented.

6.41 In addition, the evaluation identified the following issues with the model:

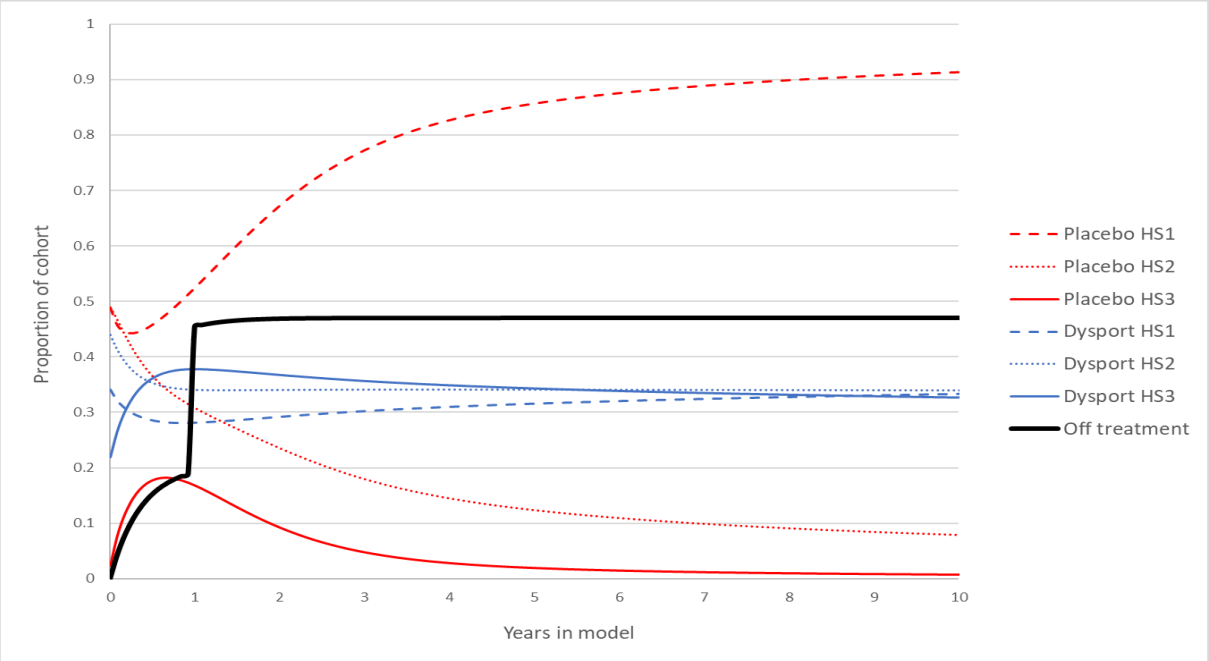
- The regressions predicted patients treated with standard of care were much more likely to transition from better health states to worse health states over time; whereas, patients treated with Dysport® were likely to transition into the better HS3 health state early – see Table 10.
- The model also assumed that patients remained in the same health state after discontinuation with Dysport®. This meant fewer patients transitioned to worse health states in the Dysport® arm over time – see Table 10 and Figure 2.

Table 10: Comparison of health state distribution in trial data and predicted in the model (base case)

	HS1			HS2			HS3		
Day	Model	Trial	Diff	Model	Trial	Diff	Model	Trial	Diff
Placebo									
0									
28									
56									
84									
112									
140									
168									
Dysport									
0: submission Pre-PBAC									
28: submission Pre-PBAC									
56: submission Pre-PBAC									
84: submission Pre-PBAC									
112: submission Pre-PBAC									
140: submission Pre-PBAC									
168: submission Pre-PBAC									
196: submission Pre-PBAC									
224: submission Pre-PBAC									
252: submission Pre-PBAC									
280: submission Pre-PBAC									
308: submission Pre-PBAC									

Source: compiled during the evaluation from "Section 3 Economic analysis workbook.xlsx" and Table 1, p2 of the Pre-PBAC Response

Figure 2: Markov trace of model health states and the proportion on treatment, by arm and cycle (base case)



Source: compiled during the evaluation from "Section 3 Economic analysis workbook.xlsx".

6.42 The decline in walking speed and associated reduction in quality of life predicted for standard of care compared to Dysport® in combination with the nominated 10 year time horizon were the key drivers of the model – see Table 11.

Table 11: Key drivers of the model

Description	Method/Value	Impact
Extrapolation	Ordered logit regressions fitted to 'change' in health states (up or down) in trial data to predict change in health states over 10 years. The regressions predicted walking speed would decline over time for patients treated with standard of care, but improve and stabilise for patients treated with Dysport plus standard of care.	High, favours Dysport
Time horizon	Assumed 10-year time horizon. Given the model predicted walking speed declined over time for patients treated with standard of care alone but did not decline for Dysport, incremental benefits continually accrued and increased over time.	High, favours Dysport

Source: compiled during the evaluation.

6.43 The PBAC noted that given the substantial uncertainty surrounding the long term impact of Dysport® treatment, a five year time horizon would be more appropriate.

6.44 Table 12 provides the results of the stepped economic evaluation, as presented in the submission.

Table 12: Results of the stepped economic evaluation

Step and component	Proposed medicine	Comparator	Increment
Step 1: 'trial-based' costs and outcomes# - ITT population; time horizon 0.25 of a year; observed distribution across health states in Study 140/142; observed discontinuation in Study 140/142			
Costs	$[redacted]	-	$[redacted]
QALYs	0.1449	0.1412	0.0037
Incremental cost/extra QALY gained			$[redacted]#
Step 2: time horizon extended to 1 year# - ITT population; time horizon 1 year; observed distribution across health states in Study 140/142; observed discontinuation in Study 140/142			
Costs	$[redacted]	-	$[redacted]
QALYs	0.4990	0.4906	0.0085
Incremental cost/extra QALY gained			$[redacted]
Step 3: subgroup - Subgroup (event ≤2 years); time horizon 1 year; observed distribution across health states in Study 140/142 observed discontinuation in Study 140/142*			
Costs	$[redacted]	-	$[redacted]
QALYs	0.4974	0.4805	0.0169
Incremental cost/extra QALY gained			$[redacted]
Step 4: time horizon extended to 10 years (5% discounting) - Subgroup (event ≤2 years); time horizon 10 year (5% discounting); observed (Study 140/142) then parametric distribution across health states in Study 140/142; observed (Study 140/142) then parametric discontinuation in Study 140/142			
Costs	$[redacted]	-	$[redacted]
QALYs	3.7921	3.4001	0.3920
Incremental cost/extra LYG gained			$[redacted]
Step 5: complete parametric analysis - Subgroup (event ≤2 years); time horizon 10 year; parametric distribution across health states; parametric discontinuation			
Costs	$[redacted]	-	$[redacted]
QALYs	3.8313	3.4002	0.4311
Incremental cost/extra QALY gained (base case)			$[redacted]

Error in starting distributions corrected during the evaluation. Cells L29:N29 and T29:V29 corrected to reflect health state distributions at baseline in the ITT population, rather than the subgroup.

* Different discontinuation rates between ITT and subgroup populations resulted in differences in costs and QALYs.

Source: Table 3.18, p152 of the submission.

The redacted table shows ICERs in the range of $45,000/QALY - $75,000/QALY to more than $200,000/QALY.

6.45 The ESC considered that the model results were not supported by evidence presented in the submission, particularly in terms of the persistent decline in active functioning and quality of life from baseline predicted for standard of care patients. Patients who received placebo in Study 140 demonstrated improved MAS score and walking speed relative to baseline, and mean PGA score at Week 4 was positive (indicating improvement from baseline). There were no differences in short-term quality of life in any of the trials presented in the submission (Study 140, Johnson et al 2004). Longitudinal data in Gillard et al 2015 indicated average quality of life improved over time (0.59 to 0.64 over two years) with standard of care (although it was not reported whether standard of care included botulinum toxin). The PSCR acknowledged the discrepancy between walking speeds observed in the trials for placebo patients and

the predicted decline in the economic model, and provided results for sensitivity analyses assuming (i) matched initial distribution of walking speeds in the Dysport® and placebo arms using Study 140 and Study 142 (ICER range: $45,000 - $75,000); and (ii) no placebo transitions (Study 140 and Study 142, ICER range: $75,000 - $105,000). The ESC considered that the sensitivity analyses which matched initial distributions provided a reasonable proxy for the base case ICER.

6.46 The ESC considered that modelling a waning of the effect of Dysport® would be appropriate and that utilisation data show greater discontinuation than was estimated in the model. The pre-PBAC response stated that the model incorporated a waning effect for Dysport® through the inclusion of a time dependent variable.

6.47 The ESC noted also that the model structure did not account for the natural history of stroke, which may include subsequent strokes not resulting in death, but that may lead to discontinuation of treatments. The pre-PBAC response contented that as patients were withdrawn from the study if they experienced a subsequent stroke or TBI, the resulting discontinuation of treatment was intrinsically included in the discontinuation rates in the model.

6.48 A range of sensitivity analyses were conducted as part of the evaluation. The results indicated that the model was sensitive to the ordered logit regressions, time horizon, and discontinuation rates/stopping rule. The PBAC noted that the sensitivity analyses do not account for the correction of the initial distribution of patients across health states, as provided in the pre-PBAC response, and therefore underestimate the ICER.

6.49 As discussed above, the model predicted that walking speed for patients treated with standard of care (placebo) continually declined over time; however, patients treated with Dysport® accrued early gains which were maintained for the duration of the model. As there was no explicit relationship between response and continued treatment in the model, and patients were assumed to maintain their response after stopping Dysport®, the optimal strategy was to limit treatment of Dysport® to one cycle (ICER = less than $15,000/QALY). The PBAC considered that this highlighted the substantial uncertainty within the model and the concerns regarding whether the model was appropriately structured to estimate the cost-effectiveness of Dysport®.

Drug cost/patient/year: $5,028.13 (Dysport® 1500U)

6.50 In the modelled economic evaluation, the average cost of treatment (Dysport® plus administration) per patient per year (364 days), was $5,027.76 (or $5,028.13 with updated DPMQ). This assumed that the patient remained on therapy and received 2.66 vials of 500U every 16.13 weeks. The cost in the first year of the model was slightly higher ($5,427.38) given re-treatment could occur from Week 12. The median duration of treatment for focal spasticity cited in the DUSC review was one year.

Estimated PBS usage & financial implications

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

6.52 The submission used an epidemiological approach to estimate the prevalent and future incident populations for patients with lower limb spasticity following an acute event (e.g. stroke, TBI, spinal cord injury). Eligible patients were calculated from AIHW hospital data, the Australian Spinal Cord Injury Register, and a Sponsor advisory board meeting.

6.53 Table 14 summarises the estimated use and associated financial implications of listing Dysport® on the PBS. The net cost to the PBS over the first six years was estimated to be more than $100 million (updated DPMQ); the net cost to the MBS for administration over the first six years was estimated to be less than $10 million.

Table 14: Estimated use and financial implications

		Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
A	Australian aged 18+	19,853,831	20,173,593	20,492,073	20,813,398	21,139,340	21,474,344
B	Eligible incident patients with LL spasticity#	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	TBI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C	Eligible prevalent patients with LL spasticity*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
D	Total eligible patients receiving treatment (B+C)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
E	Number of 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 (25.4%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dysport 500U (74.6%)	[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 PBS/RPBS cost**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**
J	**Net cost to MBS¥**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**
K	**Net change to government budget**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**

Abbreviations: LL=lower limb; MAS=modified Ashworth scaler; SCI=spinal cord injury; TBI=traumatic brain injury

Incident patients=incidence rate x (proportion resulting in spasticity) x (proportion with LL spasticity x proportion with MAS (2-4)) 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 proportion not permanently discontinued in Yr 1 (80%) x responded after 4 cycles (82.4%) x annual mortality (Yr1: 17.6%, Yr2-Yr6: 2.89%)

^ Based on the rate of re-treatment (3.855114/378.8352) over 365.25 days

‡ Dispensed price calculated during the evaluation using PBAC pricing calculator version 28 (DPMQ for 300U is $1515.49 and 500U is $1618.53)

¥ An error in the EXCEL worksheet (applying 85% benefit to both private and public services) was corrected during the evaluation with the appropriate percentage of benefit to private services (75%)

Source: Constructed during the evaluation from Section 4 of the submission and Section 4 Financial implications workbook.xlsx

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

6.54 The DUSC regarded the accuracy of the estimated net cost of the proposed listing to the PBS as uncertain, stating that the eligible population may have been underestimated, but that the average duration of treatment with Dysport® may have

been overestimated. The DUSC noted that a sensitivity analysis that increased the proportion of patients with spasticity and reduced the average duration of treatment resulted in similar expenditure in Year 6.

6.55 The DUSC noted that the number of treatment cycles per year (3.72) was based on the treatment of patients with spasticity following stroke, and may be higher for patients with TBI or spinal cord injury. The DUSC also stated that the estimates of discontinuation and response after four cycles, also based on stroke patients, may differ for TBI and spinal cord injury patients.

6.56 The PBAC agreed with the DUSC that extrapolation of utilisation estimates based on stroke patients to TBI and spinal cord injury patients remained uncertain. The PBAC was also concerned that the financial implications may be affected by the use of Dysport® across multiple focal points and in patients with concurrent upper limb and lower limb focal spasticity.

Financial Management – Risk Sharing Arrangements

6.57 None proposed. The submission stated the Sponsor was willing to enter into a Risk Sharing Arrangement due to a risk of leakage of Dysport® use in populations outside of the requested restriction such as in patients with spasticity due to non-acute aetiologies.

Quality use of medicines

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

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

7 PBAC Outcome

7.1 The PBAC did not recommend the PBS listing of Clostridium botulinum type A toxin-haemagglutinin complex (Dysport®) for the treatment of adult patients with moderate to severe spasticity of the lower limbs following an acute event 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 impact estimations.

7.2 The PBAC acknowledged the consumer comments, which were supportive of listing Dysport® for lower limb spasticity following an acute event and considered the advice received during the sponsor hearing to be informative. The PBAC concluded that there was a clinical need for treatments of lower limb focal spasticity following an acute event.

7.3 The PBAC noted that the key trial, Study 140, consisted of a single injection during a randomised, double-blind phase, followed by up to four treatments in an open label extension, Study 142. The PBAC considered there was a lack of comparative evidence

beyond the first injection, and insufficient evidence to inform the benefit of continuing therapy, 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; and
- related to muscles other than the gastrocnemius soleus complex. The PBAC considered that based on biological plausibility, the effect of Dysport® could be extrapolated to other muscle groups.

7.4 The PBAC considered that, although standard of care/placebo was an appropriate comparator, botulinum toxin type-A (BOTOX®) may be an appropriate near market comparator.

7.5 The PBAC noted that the primary outcome of the key trial, which was a reduction in Modified Ashworth Scale (MAS) score of at least one, was not consistent with the PBS continuation criteria for Dysport® use in the treatment of focal spasticity following stroke in the upper limb, which required a reduction in MAS of greater than one.

7.6 The PBAC considered that Dysport® was not superior compared to placebo in terms of effectiveness in the treatment of focal spasticity of the lower limb following an acute event. Although the key trial demonstrated a small, statistically significant improvement in MAS score at Weeks 4 and 12, the results were not clinically significant as they did not exceed the predefined minimal clinically important difference (MCID) of at least one MAS point. The PBAC also noted the non-significant difference in the proportion of responders. The PBAC considered that efficacy data from the supportive trials in terms of change in MAS were inconsistent.

7.7 The PBAC noted that change in MAS score was not used to inform the economic model. Instead, change in walking speed, as measured by the 10 m comfortable barefoot walking test was used. It was noted that there were no significant differences between Dysport® and placebo in terms of walking speed at Week 4 or 12 in the key trial, Study 140. The PBAC considered that data from the supportive trials were inconsistent in terms of the type of test used to measure walking speed and the outcomes reported.

7.8 The PBAC considered that Dysport® was inferior in terms of safety compared to placebo.

7.9 The PBAC considered that the premise of the economic evaluation was flawed as it modelled an improvement in walking speed, which was based on a *post-hoc* subgroup analysis of a non-statistically different outcome, and a consequential improvement in quality of life, which was not demonstrated in the trial, for patients treated with Dysport®. This resulted in a highly uncertain ICER. The PBAC considered that a more appropriate economic evaluation would be based on the primary outcome of the trial (change in MAS) and would also be consistent with the continuation criteria in the proposed restriction.

7.10 In addition, the PBAC were concerned that the economic model was not appropriately structured to estimate cost-effectiveness, and considered that the structural issues identified by the evaluation and ESC should be addressed in any resubmission.

7.11 The PBAC, noting the advice from DUSC, considered that the utilisation estimates were uncertain. The PBAC were also concerned by the uncertainty surrounding the extrapolation of utilisation estimates from stroke patients to those with focal spasticity due to other aetiologies, and the potential effects of Dysport® use across multiple focal points in both the upper and lower limbs. Given these uncertainties in utilisation, any future submission for lower limb focal spasticity following an acute event should consider proposing an utilisation cap.

7.12 The PBAC considered that the uncertainty surrounding the treatment effect of Dysport® 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. 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).

7.13 In considering the proposed listing, the PBAC:

- Advised that the PBS eligibility criteria should remain consistent with that of the upper limb, and restrict use of Dysport® to patients with a MAS score of 3 or more at baseline;
- Determined that the timing of the onset of treatment should be at the discretion of the physician;
- Noted that the proposed continuation criteria, which was based on a reduction in MAS of at least one was consistent with the clinical evidence presented in the submission, but was inconsistent with the current restriction for upper limb spasticity following a stroke, which requires a reduction in MAS of greater than one. The PBAC considered that further clinical input would be informative, while being of a mind to ensure consistency of the restriction with the trial evidence. The PBAC noted that this may have implications for upper limb spasticity restrictions and that similar input on Dysport® use in upper limb spasticity would also be helpful; and
- Noted that the frequency of retreatment was likely to be variable depending on response and was not informed by evidence presented in the submission. The PBAC considered expert opinion that indicated that the reinjection interval increased with continued treatment and determined 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.

7.14 The PBAC advised that any subsequent submission should be a major submission and should address the recommended changes to the restriction, the economic model and

the PBAC's cost-effectiveness concerns. The PBAC considered that a significant reduction in price would be required for it to accept cost-effectiveness.

7.15 The PBAC noted that this submission is eligible for an Independent Review.

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 will continue to work with the PBAC and Department of Health to ensure timely access for those patients who will most benefit from treatment with Dysport.