

## **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 submission**

- 1.1 The submission requested Section 100 Botulinum Toxin Program listing for clostridium botulinum Type A toxin-haemagglutinin complex, hereafter named Dysport®, for the treatment of moderate to severe focal spasticity of the upper limb in patients with cerebral palsy in patients aged 2 years and older.
- 1.2 Listing was requested on the basis of a cost-minimisation analysis versus botulinum toxin, type A purified neurotoxin complex, hereafter named Botox®. The table below provides the components of the clinical issues addressed by the submission.

**Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)**

<b>Component</b>	<b>Description</b>
Population	Moderate to severe upper limb spasticity in cerebral palsy patients aged 2 to 17 years and adults 18 years and older
Intervention	Clostridium botulinum type A toxin-haemagglutinin complex (Dysport®)
Comparator	Botulinum toxin, type A purified neurotoxin complex (Botox®)
Outcomes	Spasticity as measured by Modified Ashworth Scale (MAS), Goal Attainment Scale (GAS), adverse events
Clinical claim	For the treatment of moderate to severe upper limb spasticity in cerebral palsy patients, Dysport® is as effective as Botox® at improving muscle tone and spasticity with a comparable safety profile.

Source: Table 1-1, p16 of the submission.

### **2 Background**

#### **Registration status**

- 2.1 Dysport® was considered by the TGA at the 21 June 2020 Advisory Committee on Medicines meeting at which the ACM considered that the product had an overall positive benefit-risk profile for the symptomatic treatment of upper limb focal spasticity in children aged 2 years and older. The Delegate's decision was not available at the time of PBAC consideration. Dysport® currently has TGA approval for treatment of this condition in adults.
- 2.2 Dysport® is TGA approved for treatment of focal spasticity of the lower limbs in children, focal spasticity of the upper and lower limbs in adults, spasmodic torticollis, blepharospasm, hemifacial spasm and glabellar lines.

***MSAC consideration***

- 2.3 The PBAC noted that the sponsor has lodged a minor streamlined codependent submission to the Medical Services Advisory Committee (MSAC) for its July 2020 meeting. Application 1610 requests changes to the item descriptor of MBS item 18361, to include ‘Clostridium Botulinum Type A Toxin-Haemagglutinin Complex (Dysport)’ in the list of botulinum toxins associated with the item number, as well as minor amendments to align the descriptor with the current PBS listing.

***Previous PBAC consideration***

- 2.4 While Dysport® has not been previously considered by the PBAC for treatment of upper limb spasticity in patients with cerebral palsy, it has been considered numerous times for other upper and lower limb spasticity-related conditions. A summary of those submissions is provided in the table below. Also provided is a list of Botox® submissions for upper and lower limb spasticity-related conditions.

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**Table 2: Listing of Dysport® and Botox® submissions for upper and lower limb spasticity-related conditions**

Date	Requested listing	PBAC decision
<b>Dysport® submissions</b>		
September 2001	Treatment of spasticity of the arm in adults following a stroke.	Rejected
September 2002 (resubmission)	Treatment of moderate to severe spasticity of the arm following a stroke.	Rejected
November 2007	Treatment of moderate to severe spasticity of the upper limb in adults following a stroke as an adjunct to physical therapy.	Recommended; maximum number of treatments is 4 per upper limb and per lifetime.
November 2018	Treatment of adults with lower limb focal spasticity, following an acute event that occurred ≤2 years prior to treatment.	Rejected
November 2018	Extension of PBS listing to adult patients with non-stroke upper limb focal spasticity. Requested removal of the maximum limit of four-treatments per limb per lifetime restriction.	Rejected
March 2019 (minor resubmission)	As per November 2018 for upper limb.	Recommended
July 2019 (resubmission)	Treatment of adult patients with moderate to severe spasticity of the lower limb following an acute event.	Recommended
<b>Botox® submissions</b>		
November 2005	Treatment of focal spasticity in adults	Rejected
July 2006 (resubmission)	Treatment of focal spasticity in the upper or lower limb of adults who have failed other treatments.	Rejected
July 2008 (resubmission)	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.	Recommended; maximum number of treatments is 4 per upper limb and per lifetime.
July 2008 (resubmission)	Treatment of moderate to severe spasticity of the lower limb in ambulatory adults following a stroke as second line therapy when standard management has failed or as adjunct to physical therapy.	Rejected
November 2008	Treatment of moderate to severe spasticity of the upper limbs of children (2 years of age or older) with cerebral palsy.	Recommended
July 2009 (minor)	Treatment of moderate to severe spasticity of the upper limb in adults with multiple sclerosis, traumatic brain injury and spinal cord injury as an adjunct to physical therapy.	Rejected
November 2018	Treatment of adults with moderate to severe lower limb focal spasticity following an acute event.	Deferred
March 2019 (minor resubmission)	Lower limb spasticity following an acute event.	Recommended
November 2019 (minor)	Expansion of the current listing for the treatment of moderate to severe focal spasticity of the upper limb following a stroke to also include spasticity following acute events other than stroke.	Recommended

Source: PSDs for each item from 2005 onward; items prior to 2005 sourced from Table CIC.1, 6.02.COM November 2018.

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

### 3 Requested listing

Name, restriction, manner of administration, form	Max qty	No. of repeats	Dispensed price for max qty	Proprietary name and manufacturer
Clostridium botulinum type A toxin-haemagglutinin complex, 300 unit injection, 1 vial	4	-	\$1,221.95	Dysport® Ipsen Pty Ltd
Clostridium botulinum type A toxin-haemagglutinin complex, 500 unit injection, 1 vial	2	-	\$1,094.89	Dysport® Ipsen Pty Ltd

<b>Category/Program:</b>	Section 100 - Botulinum Toxin Program
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	Episodic
<b>Severity:</b>	Moderate to severe
<b>Condition:</b>	Focal spasticity of the upper limb in patients with cerebral palsy
<b>PBS Indication:</b>	Moderate to severe spasticity of the upper limb
<b>Treatment phase:</b>	Initial and continuing
<b>Restriction:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required – Telephone, Electronic <input checked="" type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	Must be treated by a neurologist; OR Must be treated by an orthopaedic surgeon; OR Must be treated by a paediatrician; OR Must be treated by a rehabilitation specialist; OR Must be treated by a plastic surgeon
<b>Clinical criteria:</b>	Patient must have cerebral palsy.
<b>Population criteria:</b>	Patient must be aged for 2 to 17 years inclusive OR Patient must be aged 18 years or older
<b>Administrative Advice:</b>	The units used to express the potency of botulinum toxin preparations currently available for PBS subsidy are not equivalent
<b>Cautions:</b>	Contraindications to treatment include known sensitivity to botulinum toxin

- 3.1 The requested price is the same as that for the Dysport® PBS listing for upper limb focal spasticity following an acute event in adults. The requested listing, which is limited to patients with cerebral palsy, is narrower than the proposed TGA indication, which does not limit use based on clinical criteria.
- 3.2 The current PBS listing for upper limb spasticity following an acute event requires that patients respond to treatment, and that there must not be more than 4 treatment periods in the first year of treatment, and no more than 2 treatment periods per upper limb each year thereafter. Such criteria are not applicable to the requested listing.
- 3.3 As noted by the submission, the requested restriction is consistent with the current PBS listing for Botox® for upper limb focal spasticity in patients with cerebral palsy. While the PBS indication, restriction category (Streamlined) and treatment criteria are identical across Dysport® and Botox®, the requested Dysport® listing differs slightly from the Botox® listing in that the Botox® listing uses two separate population criteria for paediatric and adult patients while the requested Dysport® listing uses one, with

an 'OR'. The PBAC considered that the Dysport® restriction should be consistent with the current Botox® restrictions.

- 3.4 The submission did not propose a grandfather restriction. There was no discussion of grandfathering in the submission and grandfathered patients were not included in the financial estimates.

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

## **4 Population and disease**

- 4.1 Spasticity is a chronic manifestation of upper motor neuron syndrome due to lesions of the pyramidal tract (an aggregation of upper motor neurons). The most common cause of the central nervous system (CNS) lesions leading to paediatric upper limb spasticity is cerebral palsy. The submission cited literature (Delgado 2010; Ronan 2007) stating that the majority of children with cerebral palsy are affected by spasticity, which can be defined as hypertonia in which one or both of the following signs are present: 1) resistance to externally imposed movement increases with increasing speed of stretch and varies with the direction of joint movement; 2) resistance to externally imposed movement rises rapidly above a threshold speed of joint angle.

- 4.2 The submission added description of the impact of spasticity, saying that particularly in the upper limbs, the increased muscle tone impairs the reach, grasp, manipulation and release, leading to restriction in everyday life and educational activities. The inability to fully use the affected arm(s) for bimanual activities prohibits the development of independent functioning in daily life. The submission noted that impaired arm function prevents children from fully engaging in social, educational and leisure roles. Consequently, reduction of the increased muscle tone and spasticity is important not only for the prevention of fixed muscle contractures and deformities but may also be important for the improvement of the motor ability and functional skills of the children. While the requested PBS listing includes an adult population, the submission did not provide any discussion of goals of treatment in an adult population.

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

## **5 Comparator**

- 5.1 The submission nominated Botox®, another botulinum toxin type A (BoNT-A), as the main comparator. The main reasons provided for this nomination were: Botox® is the only BoNT-A that is currently PBS-listed for moderate to severe spasticity of the upper limb in patients with cerebral palsy; and given that Botox® is PBS-listed in the same target population and is in the same therapeutic class as Dysport®, it is the medicine most likely to be replaced by Dysport®. Botox® is the appropriate comparator.

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

## **6 Consideration of the evidence**

### ***Sponsor hearing***

6.1 There was no hearing for this item.

### ***Consumer comments***

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

### ***Clinical trials***

6.3 The submission was based on indirect comparisons between one Dysport® trial, Study 153, and five Botox® trials (Fehlings 2018; Fehlings 2000; Rameckers 2009/Speth 2005; Lowe 2006; Olesch 2010). While the submission identified seven Botox® trials, and included baseline demographic information, a risk of bias assessment, outcome description and safety and effectiveness results for all seven trials, two trials (Russo 2007; and Wallen 2007) were appropriately excluded due to the doses of Botox® used from the indirect comparisons.

6.4 Details of the trials presented in the submission are provided in the table below.

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Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
<b>Dysport®</b>		
Study 153	A Phase 3, multicentre, double blind, prospective, randomised, controlled, multiple treatment study assessing efficacy and safety of Dysport® used in the treatment of upper limb spasticity in children. Shierk A, Jiménez-Moreno AC, Roberts H, Ackerman-Laufer S, Backer G, Bard-Pondarre R, Cekmece C, Pyrzanowska W, Vilain C, Delgado MR. Development of a pediatric goal-centered upper limb spasticity home exercise therapy program for use in a Phase-III trial of abobotulinumtoxina (Dysport®). Novak I. Commentary on development of a pediatric goal-centered upper limb spasticity home exercise therapy program.	CSR 153 2019  <i>Phys Occup Ther Pediatr.</i> 2019; 39(2):124-135.  <i>Phys Occup Ther Pediatr.</i> 2019; 39(2):136-138.
<b>Botox®</b>		
Fehlings 2018	Fehlings DGM. Efficacy and safety of onabotulinumtoxina for the treatment of pediatric upper limb spasticity: primary results. Fehlings DGM. Efficacy and safety of onabotulinumtoxina for the treatment of pediatric upper limb spasticity: primary results.	<i>Dev Med Child Neurol</i> 2018; 60(S3):33-34. 4th Int Congress INA, Copenhagen, Denmark 2019; poster P3.20.
Fehlings 2000	Fehlings D, Rang M, Glazier J et al. An evaluation of botulinum-A toxin injections to improve upper extremity function in children with hemiplegic cerebral palsy.	<i>J Pediatr</i> 2000; 137(3):331-337.
Lowe 2006	Lowe K, Novak I, Cusick A. Low-dose/high-concentration localized botulinum toxin A improves upper limb movement and function in children with hemiplegic cerebral palsy.	<i>Dev Med Child Neurol</i> 2006; 48(3):170-755.
Olesch 2010	Olesch CA, Greaves S, Imms C, Reid SM, Graham HK. Repeat botulinum toxin-A injections in the upper limb of children with hemiplegia: a randomized controlled trial.	<i>Dev Med Child Neurol</i> 2010; 52(1):79-86.
Rameckers 2009/ Speth 2005 <sup>a</sup>	Rameckers EA, Speth LA, Duysens J, Vles JS, Smits-Engelsman BC. Botulinum toxin-a in children with congenital spastic hemiplegia does not improve upper extremity motor-related function over rehabilitation alone: a randomized controlled trial. Speth LA, Leffers P, Janssen-Potten YJ et al. Botulinum toxin A and upper limb functional skills in hemiparetic cerebral palsy: a randomized trial in children receiving intensive therapy.	<i>Neurorehabil Neural Repair</i> 2009; 23(3):218-25.  <i>Dev Med Child Neurol</i> 2005; 47(7):468-73.

Source: Table 2-5, p39-40 of the submission.

<sup>a</sup> Rameckers 2009 and Speth 2005 are two publications of the same trial. The submission indicated that where outcomes were not available in Rameckers 2009, values from Speth 2005 were used.

6.5 The key features of the evidence included in the indirect comparisons are summarised in the table below.

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Table 4: Key features of trials included in the indirect comparisons

Trial	N	Design/duration	Risk of bias	Patient population	Outcomes	Use in cost-minimisation
<b>Dysport® vs. no intervention (2 U/kg dose)</b>						
Study 153	210	R, DB, MC; 4 treatment cycles (16 weeks)	Low	Age 2 to 17 years; weight ≥ 10kg; cerebral palsy and increased muscle tone/spasticity in ≥ 1 upper limb	MAS, PGA, TAS	Used
<b>Botox® vs. no intervention</b>						
Fehlings 2018	235	R, DB (12 weeks)	Low	Age 2 to ≤ 17 years; cerebral palsy with elbow or wrist spasticity	MAS-B, CGI, GAS, MTS	Not used
Fehlings 2000	30	R, SB (6 months)	High	Age 2.5 to 10 years; hand or arm hemiplegic cerebral palsy	QUEST, MAS	Used
Rameckers 2009/ Speth 2005 <sup>a</sup>	20	R (6 months)	High	Age 4 to 16 years; spastic hemiplegia	ROM, SRA	Used (Speth 2005)
Lowe 2006	42	R, SB (6 months)	High	Age 2 to 8 years; hemiplegic cerebral palsy	QUEST, GAS	Used
Olesch 2010	24	R (16 weeks)	High	Age 1.5 to 5 years; cerebral palsy affecting upper limb activity	COPM, GAS	Not used

Source: Section 2.3.1, p42; Table 2-6, p43-44; Table 2-37, p84-85; Table 2-38, p86-89 of the submission.

COPM=Canadian Occupational Performance Measure; DB=double blind; GAS=goal attainment scale; MAS=modified Ashworth Scale; MC=multi-centre; MTS=modified Tardieu Scale; PGA=Physician's Global Assessment; QUEST=Quality of Upper Extremity Skills Test; R=randomised; ROM=range of motion; SB=single-blind; SRA=stretch restricted angle; TS=Tardieu Scale

<sup>a</sup> Rameckers 2009 and Speth 2005 are two publications of the same trial. The submission indicated that where outcomes were not available in Rameckers 2009, values from Speth 2005 were used.

- 6.6 Study 153 was a randomised, double-blind comparison of three Dysport® doses, 2 U/kg, 8 U/kg and 16 U/kg. The trial had a low risk of bias, in contrast to the Botox® trials, of which only one was double-blind (Fehlings 2018), and in most the patients or parents were aware of treatment. All trials included occupational therapy as adjunct therapy.
- 6.7 Since Study 153 did not have a 'no intervention' arm the submission used the 2 U/kg arm as the no intervention arm, as it was considered to be the equivalent of no intervention. The submission, however, also claimed that many of the indirect comparisons would bias against Dysport® as the treatment effect for 'no intervention' in Study 153 was larger than in the Botox® trials where no intervention or placebo treatment was used. It would be difficult to quantify a difference in treatment effect between the 2 U/kg Dysport® group and a no intervention group given differences across the trials. The potential impact of any bias was also difficult to measure since patients in both arms of the trials also generally received occupational therapy. It would be reasonable to conclude that any bias against Dysport® would be minimal.
- 6.8 The submission noted an independent report, the ICON report, which included a systematic literature review, feasibility assessment and statistical analysis that had been conducted in support of the indirect comparisons presented in the submission. Much of the material in the submission is the same as that presented in the ICON report.

### ***Comparative effectiveness***

- 6.9 The submission provided detailed within-trial results for each trial included in the indirect comparisons; however, the submission's presentation of results for the indirect comparisons was limited. The submission provided forest plots and brief discussions in the text, but there was no information provided as to the number of patients in each arm of the comparisons, or the values used for each outcome from each arm of the included trials.
- 6.10 As the submission's clinical claim was based solely on the indirect comparisons, those are the focus of consideration of the evidence. The submission acknowledged that the evidence presented was based on children, and there is no clinical data available to support the adult population, which is part of the requested restriction. The Pre-Sub-Committee Response (PSCR) stated that the initial PBAC recommendation for Botox® in 2008 was based on studies which included patients under the age of 18 only (Lowe, 2006; Wallen, 2007; and Fehlings, 2000) and that the PBAC stated "Patients who commenced PBS-subsidised treatment for this condition before their eighteenth birthday should be permitted to continue treatment into adulthood", which was a pragmatic decision that recognised that cerebral palsy patients do not cease suffering from spasticity at 18 years of age. In addition, the PSCR noted that the removal of the requirement that adult cerebral palsy patients must have commenced treatment with botulinum as a paediatric patient was also for pragmatic reasons, following correspondence from the RMSANZ. The PSCR requested that the same level of pragmatism be applied to this submission. The ESC considered that, provided fixed contractures had not developed, there would be no clinical reason to expect a lack of effectiveness in adults and noted that, given the nature of the therapy, treatment was unlikely to continue if no effect was observed.
- 6.11 Given the presentation of the indirect comparisons by the submission was limited, tables were constructed during the evaluation that included patient numbers and results for each trial arm. Table 5 provides an outline of the indirect comparisons presented by the submission, detailing the outcomes, included trials and assessment points.

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**Table 5: Indirect comparisons presented by the submission**

Outcome	Dysport®	Botox®
<b>Effectiveness</b>		
MAS PTMG at 6 weeks and at 16 weeks	Study 153; week 6, week 16; 2 U/kg, 8 U/kg, 16 U/kg	Fehlings 2018; week 6, week 12; 3 U/kg, 6 U/kg
MAS/AS elbow or wrist at 6 weeks and at 16 weeks	Study 153; week 6, week 16; 2 U/kg, 8 U/kg, 16 U/kg	Fehlings 2000, week 4, week 12; 2-6.6 U/kg; Speth 2005, week 6, week 12; < 1-5.8 U/kg; Lowe 2006, week 4, week 12; < 8 U/kg
MAS/AS finger at 6 weeks and at 16 weeks	Study 153; week 6, week 16; 2 U/kg, 8 U/kg, 16 U/kg	Lowe 2006; week 4, week 12; < 8 U/kg
GAS score at 6 weeks and at 16 weeks	Study 153; week 6, week 16; 2 U/kg, 8 U/kg, 16 U/kg	Lowe 2006, week 4, week 12; < 8 U/kg; Olesch 2010, 16 weeks; 3 U/kg-6 U/kg
<b>Safety</b>		
Overall AEs	Study 153; week 16; 2 U/kg, 8 U/kg, 16 U/kg	Olesch 2010, 52 weeks; 3 U/kg-6 U/kg; Fehlings 2018, week 12; 3 U/kg, 6 U/kg
Serious AEs, treatment-related AEs, discontinuation due to AEs	Study 153; week 16; 2 U/kg, 8 U/kg, 16 U/kg	Fehlings 2018; week 12; 3 U/kg, 6 U/kg

Source: Table 2-77, p132; Table 2-78, p132 of the submission.

AEs=adverse events; AS=Ashworth Scale; GAS=Goal Attainment Scale; MAS=Modified Ashworth Scale; PTMG=primary target muscle group

- 6.12 The Modified Ashworth Scale (MAS), the Ashworth Scale (AS) and the Goal Attainment Scale (GAS) are scales that have been used in numerous PBAC submissions for lower and upper limb spasticity. The submission presented results for comparisons at both 6 and 16 weeks, but the primary outcome of Study 153 was at 6 weeks. There is some discordance of result time points, with results for the Botox® trials being at 4 and 12 weeks. The submission maintained that results at 12 weeks for Botox® and 16 weeks for Dysport® may favour Botox®, although to support this claim the submission cited only a paper with mice as the subjects (de Paiva 1999), which noted ‘...obvious difficulties in precisely comparing time courses in human and mice’, as well as a retrospective review of Dysport®.
- 6.13 The submission did not provide any discussion of a non-inferiority margin in regard of the analyses presented. The submission provided results for the Dysport® 8 U/kg group and the 16 U/kg group versus Botox®, as well as a pooled 8 U/kg and 16 U/kg group. The submission referred to the individual 8 U/kg and 16 U/kg comparisons as ‘base case’ comparisons. The table below provides the results for the indirect comparison of the MAS primary target muscle group (PTMG), the primary outcome in Study 153, at week 6 and week 16.

**Table 6: Results of the indirect comparison of Dysport® and Botox® for MAS PTMG at week 6 and week 16**

Week 6	Change from baseline in MAS PTMG (LSM <sup>a</sup> )			Difference in change from baseline (95% CI)
	Dysport®	Common reference no intervention <sup>b</sup>	Botox®	
8 U/kg Study 153	N=69 -2.0	N=69 -1.6	-	<b>-0.40 (-0.75, -0.05)</b>
16 U/kg Study 153	N=70 -2.3	N=69 -1.6	-	<b>-0.70 (-1.03, -0.37)</b>
pooled Dysport® fixed effects (I <sup>2</sup> =32.3%; p=0.22)				<b>-0.56 (-0.80, -0.32)</b>
6 U/kg Fehlings 2018	-	N=79 -1.1	N=77 -1.9	<b>-0.60 (-0.90, 0.30)</b>
3 U/kg Fehlings 2018	-	N=79 -1.1	N=78 -1.9	<b>-0.72 (-0.98, -0.46)</b>
pooled Botox® fixed effects (I <sup>2</sup> =0%; p=0.55)				<b>-0.67 (-0.87, -0.47)</b>
Indirect pooled Dysport® vs. pooled Botox® (95% CI)				0.11 (-0.20, 0.42)
Indirect Dysport® 8 U/kg vs. pooled Botox® (95% CI)				0.27 (-0.13, 0.67)
Indirect Dysport® 16 U/kg vs. pooled Botox® (95% CI)				-0.03 (-0.42, 0.36)
Week 16	Dysport®	Common reference no intervention <sup>b</sup>	Botox®	Difference in change from baseline (95% CI)
8 U/kg Study 153	N=68 -1.2	N=68 -0.9	-	<b>-0.40 (-0.75, -0.05)</b>
16 U/kg Study 153	N=68 -1.5	N=68 -0.9	-	<b>-0.60 (-0.97, -0.23)</b>
pooled Dysport® fixed effects (I <sup>2</sup> =0%; p=0.44)				<b>-0.49 (-0.75, -0.24)</b>
6 U/kg Fehlings 2018	-	NR	NR	<b>-0.40 (-0.73, -0.07)</b>
3 U/kg Fehlings 2018	-	NR	NR	<b>-0.48 (-0.76, -0.20)</b>
pooled Botox® fixed effects (I <sup>2</sup> =0%; p=0.72)				<b>-0.45 (-0.66, -0.23)</b>
Indirect pooled Dysport® vs. pooled Botox® (95% CI)				-0.05 (-0.38, 0.29)
Indirect Dysport® 8 U/kg vs. pooled Botox® (95% CI)				0.05 (-0.37, 0.46)
Indirect Dysport® 16 U/kg vs. pooled Botox® (95% CI)				-0.15 (-0.58, 0.28)

Source: Table 2-39, p90; Section 2.5.1.2.1, p103-104; Figure 2-19, p139-140 of the submission.

CI=confidence interval; LSM=least square mean; MAS=Modified Ashworth Scale; NR=not reported; PTMG=primary target muscle group; **bold**=statistically significant

<sup>a</sup> Both the submission and the Study 153 CSR provided only least square mean change from baseline values, there were no standard deviations or standard errors provided.

<sup>b</sup> In Study 153 the 2 U/kg Dysport® arm of the trial was used as the 'no intervention' arm.

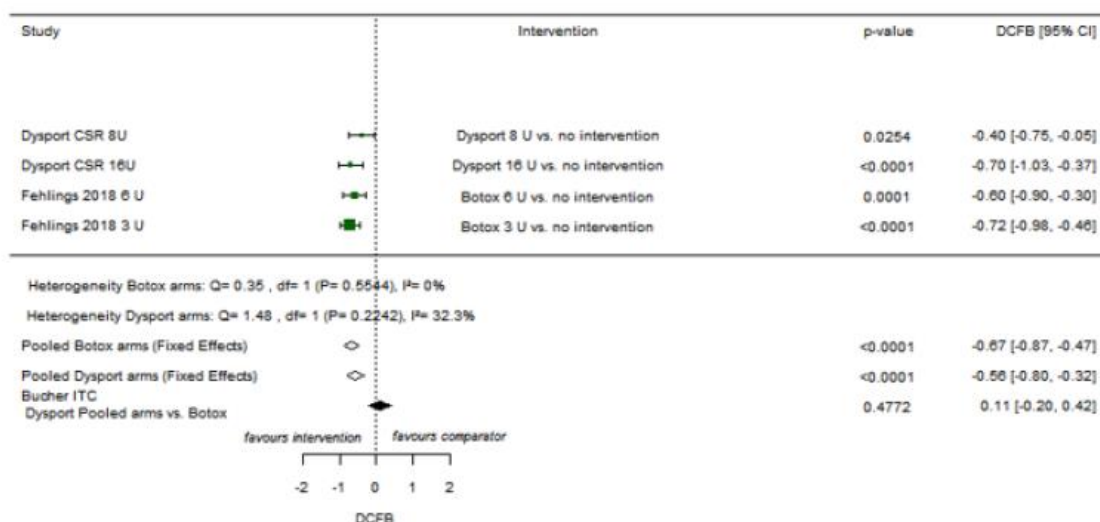
6.14 The within-trial comparisons showed statistically significant advantages for both Dysport® and Botox® compared to no intervention, and the pooled Dysport® and Botox® comparisons also showed statistically significant advantages for the active agents. The indirect comparisons showed no statistically significant difference between pooled Dysport® and pooled Botox®, at both 6 and 16 weeks. There were also no statistically significant differences between Dysport® 8 U/kg and Botox®, nor were there differences between Dysport® 16 U/kg and Botox®.

6.15 The results provided by the submission may not accurately reflect differences between Dysport® and Botox® for the primary target muscle group MAS score. While the submission identified the two dose groups in the Fehlings (2018) Botox® trial, there was only one set of results available in the poster and abstract, and these results were identified as being for both dose groups. It was not clear what data the submission used to arrive at its pooled results for Botox®. For results at 12 weeks the submission stated that MAS was significantly improved by Botox® at all assessments

throughout the 12 week study, and provided graphs from the trial’s poster, but no values for change from baseline to be used in the indirect comparisons were provided. In addition, the primary outcome in Fehlings (2018) was assessed at 4 and 6 weeks and it has been assumed that this data were used by the submission for the 6 week comparison. The 16 week comparison appeared to use 12 week data from Fehlings (2018). Finally, the no intervention group in Study 153 was the 2 U/kg Dysport® group from that trial, which was likely to have some impact on the results.

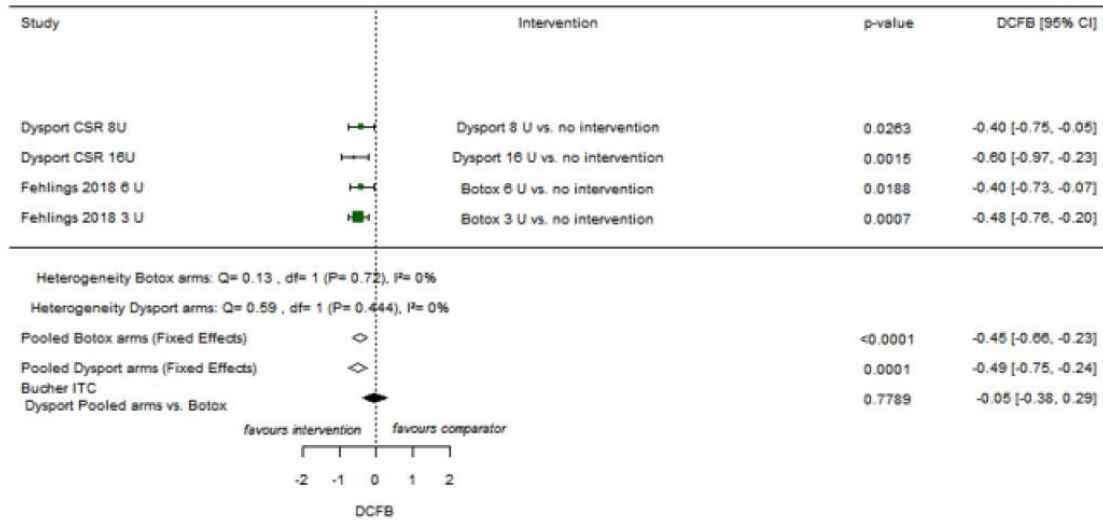
6.16 Below are the forest plots provided by the submission for the indirect comparisons.

Figure 1: Indirect comparison of pooled Dysport® and pooled Botox® at 6 weeks for MAS PTMG



Source: Figure 2-19 (A), p139 of the submission.  
 MAS=Modified Ashworth Scale; PTMG=primary target muscle group

Figure 2: Indirect comparison of pooled Dysport® and pooled Botox® at 16 weeks for MAS PTMG



Source: Figure 2-19 (B), p140 of the submission.

MAS=Modified Ashworth Scale; PTMG=primary target muscle group

6.17 The table below provides the indirect comparisons for the MAS/AS elbow outcome, with individual trial results added during the evaluation. These comparisons used Botox® data from Fehlings (2000), Rameckers 2009/Speth 2005 and Lowe (2006).

**Table 7: Results of the indirect comparison of Dysport® and Botox® for MAS/AS elbow at week 6 and week 16**

Week 6	Change from baseline in MAS/AS elbow (LSM <sup>a</sup> )			Difference in change from baseline (95% CI)
	Dysport®	Common reference no intervention <sup>b</sup>	Botox®	
8 U/kg Study 153	N=63 -1.7	N=63 -1.1	-	<b>-0.70 (-1.08, -0.32)</b>
16 U/kg Study 153	N=62 -1.9	N=63 -1.1	-	<b>-0.90 (-1.30, -0.50)</b>
pooled Dysport® fixed effects (I <sup>2</sup> =0%; p=0.48)				<b>-0.80 (-1.07, -0.52)</b>
Fehlings 2000 (4 weeks)	-	N=15 -0.20 (±0.62)	N=14 -0.29 (±0.47)	-0.09 (-0.49, 0.31)
Rameckers 2009/ Speth 2005 (6 weeks)	-	N=10 -0.4	N=10 -0.2	0.24 (-0.54, 1.02)
Lowe 2006 (4 weeks)	-	N=21 NR	N=21 NR	<b>-0.80 (-0.86, -0.74)</b>
pooled Botox® fixed effects (I <sup>2</sup> =89.2%; p=0.0001)				-0.29 (-0.94, 0.38)
Indirect pooled Dysport® vs. pooled Botox® (95% CI)				-0.51 (-1.22, 0.20)
Indirect Dysport® 8 U/kg vs. pooled Botox® (95% CI)				-0.41 (-1.17, 0.35)
Indirect Dysport® 16 U/kg vs. pooled Botox® (95% CI)				-0.61 (-1.38, 0.16)
Week 16	Dysport®	Common reference no intervention <sup>b</sup>	Botox®	Difference in change from baseline (95% CI)
8 U/kg Study 153	N=62 -0.9	N=62 -0.6	-	<b>-0.60 (-0.99, -0.21)</b>
16 U/kg Study 153	N=60 -1.1	N=62 -0.6	-	<b>-0.70 (-1.13, -0.27)</b>
pooled Dysport® fixed effects (I <sup>2</sup> =0%; p=0.74)				<b>-0.64 (-0.93, -0.36)</b>
Fehlings 2000 (12 weeks)	-	N=15 -0.37 (±0.44)	N=14 -0.23 (±0.48)	0.14 (-0.20, 0.48)
Rameckers 2009/ Speth 2005 (12 weeks)	-	N=10 -0.2	N=10 -0.4	-0.24 (-1.00, 0.52)
Lowe 2006 (12 weeks)	-	N=21 NR	N=21 NR	<b>-0.60 (-0.66, -0.54)</b>
pooled Botox® fixed effects (I <sup>2</sup> =89.4%; p=0.0001)				-0.25 (-0.83, 0.33)
Indirect pooled Dysport® vs. pooled Botox® (95% CI)				-0.39 (-1.04, 0.25)
Indirect Dysport® 8 U/kg vs. pooled Botox® (95% CI)				-0.35 (-1.05, 0.35)
Indirect Dysport® 16 U/kg vs. pooled Botox® (95% CI)				-0.45 (-1.17, 0.27)

Source: Table 2-40, p92; Table 2-53, p106; Table 2-56, p108; Figure 2-20, p141 of the submission; Table 35, p85 of Study 153 CSR; Table 3, p335 of Fehlings (2000).

AS=Ashworth Scale; CI=confidence interval; LSM=least square mean; MAS=Modified Ashworth Scale; NR=not reported; **bold**=statistically significant

<sup>a</sup> Both the submission and the Study 153 CSR provided only least square mean change from baseline values, there were no standard deviations or standard errors provided. For the Botox® trials, standard deviations were available for Fehlings (2000).

<sup>b</sup> In Study 153 the 2 U/kg Dysport® arm of the trial was used as the 'no intervention' arm. Table 2-40 (p92) of the submission only reported baseline N values, the number assessed was sourced from the Study 153 CSR.

6.18 The within-trial results for the MAS/AS elbow outcome showed statistically significant advantages for Dysport® compared to no intervention (2 U/kg) at both week 6 and week 16. For the Botox® trials the Lowe (2006) trial showed significant advantages for Botox® compared to the no intervention group, while no differences were observed for the other Botox® trials. These results were not presented or discussed by the submission, but were sourced from the forest plots. The indirect comparisons showed no statistically significant differences for Dysport® compared to Botox® at week 6 and

week 16, for the pooled comparisons and the Dysport® 8 U/kg and 16 U/kg comparisons.

6.19 There are a number of concerns with the analyses provided by the submission, including:

- the submission did not provide any patient numbers or within trial results; the evaluators derived these from the submission and the publications. The number of patients included in the analyses were relatively small, particularly in the Botox® trials (total patient numbers for each trial ranging between 20 and 42). The PSCR noted that the Botox® trials provided were the same as those provided in the original Botox® submission, with additional trials sourced as supplementary evidence;
- the week 6 analysis used 4 week data from Fehlings (2000) and Lowe (2006). The PSCR noted that the Product Information for Botox® states that clinical signs usually manifest within two to three days, clinical improvement generally occurs within the first two weeks and repeat doses should not be given more frequently than every three months. The PSCR also noted that for adult patients with focal spasticity, peak effect following treatment with either Dysport® or Botox® is observed at 4 weeks, which marginally biased against Dysport®;
- there was considerable heterogeneity in the pooled Botox® analysis at week 6 and week 16, with  $I^2=89.2%$  and  $I^2=89.4%$ , respectively. The PSCR stated that Lowe (2006) demonstrated significantly more favourable outcomes, with narrow confidence intervals, compared to the other two studies (Fehlings, 2000 and Rameckers 2009/Speth 2005) which resulted in heterogeneity across the studies. Sensitivity analyses excluding Lowe (2006) were provided (see Table 8);
- there was a lack of information for the Botox® trials around the number of Botox® injections received. While patients in the Lowe (2006) trial received a single Botox® injection, there was no information available for Fehlings (2000) and Rameckers 2009/Speth 2005. The PSCR confirmed that patients in both Fehlings (2000) and Rameckers 2009/Speth 2005 received one treatment cycle; and
- as was noted for the MAS PTMG comparisons, for Study 153 the ‘no intervention’ group was the 2 U/kg group, which was likely to impact outcomes.

6.20 The results of the sensitivity analysis excluding the Lowe (2006) trial, which, as noted in the PSCR, could have been an outlier, demonstrated that there was a statistically significant advantage for Dysport® compared to Botox® for both the 8 U/kg and 16 U/kg doses at week 6 and week 16.

Table 8: Results excluding Lowe (2006) for MAS/AS elbow

MAS/AS elbow	Week 6		Week 16	
	Difference-change from baseline (95% CI)		Difference-change from baseline (95% CI)	
	Dysport® 8 U/kg	Dysport® 16 U/kg	Dysport® 8 U/kg	Dysport® 16 U/kg
Excluding Lowe 2006	<b>-0.68 (-1.20, -0.16)</b>	<b>-0.88 (-1.42, -0.34)</b>	<b>-0.68 (-1.17, -0.18)</b>	<b>-0.78 (-1.31, -0.25)</b>

Table 2-79, p148 of the submission.

CI=confidence interval; **bold**=statistically significant

- 6.21 For the MAS/AS wrist outcome, the results followed the same pattern as that observed for MAS/AS elbow. The indirect comparisons showed no statistically significant difference between Dysport® and Botox® for the pooled comparisons and the 8 U/kg and 16 U/kg comparisons at both 6 weeks and 6 weeks. There was a statistically significant advantage observed for Botox® in the Lowe (2006) trial. As for the MAS/AS elbow outcome, there were a number of concerns with the comparisons:
- The number of patients remained small for the Botox® trials, and the patient numbers for Study 153 for Dysport® had dropped from 60+ per arm for the MAS/AS elbow comparison to 50+ per arm.
  - The week 6 analysis used week 4 data from Fehlings (2000) and Lowe (2006); it could not be determined what values were used for the Lowe (2006) trial; there was considerable heterogeneity in the pooled Botox® analyses at week 6 and week 16, with  $I^2=95%$  at both time points; there was a lack of information for the Botox® trials around the number of Botox® injections received; and for Study 153 the ‘no intervention’ group was the 2 U/kg group, which was likely to impact outcomes.
- 6.22 Results for the indirect comparison of the MAS/AS finger showed no statistically significant difference between pooled Dysport® and Botox®, and there were also no statistically significant differences between Dysport® 8 U/kg and 16 U/kg compared to Botox®. As for the MAS/AS comparisons for elbow and wrist, the results are limited by the small number of patients providing data, with between 19 and 23 patients in each arm of Study 153, and 21 patients in each arm of the Lowe (2006) Botox® trial. Also, as for the elbow and wrist comparisons, the data used for Lowe (2006) comparison could not be sourced.
- 6.23 The indirect comparisons of Dysport® and Botox® using the GAS score are based on Study 153 and Lowe (2006) at the 6 week time point, with data from Olesch (2010) added to the Lowe (2006) data for the comparison at 16 weeks. The table below provides the results of the comparisons, with patient numbers and individual trial results added during the evaluation.

**Table 9: Results of the indirect comparison of Dysport® and Botox® for GAS score at week 6 and week 16**

Week 6	Change from baseline in GAS (LSM (SD))			Difference in change from baseline (95% CI)
	Dysport®	Common reference no intervention <sup>a</sup>	Botox®	
8 U/kg Study 153	N=66 52.6 (1.2)	N=68 52.1 (9.9)	-	0.50 (-2.83, 3.83)
16 U/kg Study 153	N=70 52.6 (1.2)	N=68 52.1 (9.9)	-	0.50 (-2.83, 3.83)
pooled Dysport® fixed effects ( $I^2=0\%$ ; $p=1^b$ )				0.50 (-1.85, 2.85)
Lowe 2006 (4 weeks)	-	N=21 40.5 (2.6) <sup>c</sup>	N=21 57.8 (3.0) <sup>c</sup>	<b>20.30 (18.60, 22.0)</b>
Indirect pooled Dysport® vs. Botox® (95% CI)				<b>-10.00 (-22.70, -16.00)</b>
Indirect Dysport® 8 U/kg vs. Botox® (95% CI)				<b>-19.80 (-23.53, -16.07)</b>
Indirect Dysport® 16 U/kg vs. Botox® (95% CI)				<b>-19.80 (-23.53, -16.07)</b>
Week 16	Dysport®	Common reference no intervention <sup>a</sup>	Botox®	Difference in change from baseline (95% CI)
8 U/kg Study 153	N=23 54.2 (1.3)	N=66 55.1 (1.3)	-	-0.90 (-4.50, 2.70)
16 U/kg Study 153	N=19 55.7 (1.3)	N=66 55.1 (1.3)	-	0.60 (-3.00, 4.20)
pooled Dysport® fixed effects ( $I^2=0\%$ ; $p=0.56$ )				-0.15 (-2.70, 2.40)
Lowe 2006 (12 weeks)	-	N=21 46.8 (2.7) <sup>c</sup>	N=21 61.0 (3.8) <sup>c</sup>	<b>17.20 (15.21, 19.19)</b>
Olesch (2010)	-	N=11 48.1 (10.1)	N=11 54.1 (9.8)	6.00 (-2.32, 14.32)
pooled Botox® fixed effects ( $I^2=84.8\%$ ; $p=0.01$ )				<b>12.36 (1.48, 23.23)</b>
Indirect pooled Dysport® vs. pooled Botox® (95% CI)				<b>-12.51 (-23.68, -1.34)</b>
Indirect Dysport® 8 U/kg vs. pooled Botox® (95% CI)				<b>-18.10 (-29.56, -6.64)</b>
Indirect Dysport® 16 U/kg vs. pooled Botox® (95% CI)				<b>-16.60 (-28.06, -5.04)</b>

Source: Table 2-57, p110; Table 2-29, p113; Figure 2-23, p144-145 of the submission.

CI=confidence interval; GAS=Goal Attainment Scale; LSM=least square mean; NR=not reported; **bold**=statistically significant

<sup>a</sup> In Study 153 the 2 U/kg Dysport® arm of the trial was used as the 'no intervention' arm.

<sup>b</sup> As reported in Figure 2-23, p144-145 of the submission.

<sup>c</sup> No information was provided as to which GAS values from Lowe (2006) were used. The submission stated (p144) that GAS was measured by the family or therapist in Lowe (2006) but the submission did not indicate if the family GAS, therapist GAS or combined GAS scores were used. For this table, the therapist GAS scores have been provided

6.24 The analyses of change from baseline in GAS score showed that Botox® was statistically significantly more effective than Dysport® at improving GAS score, for all indirect comparisons. These results were influenced by the Lowe (2006) trial, as when it was removed from the week 16 analysis there was no longer a statistically significant difference between Dysport® and Botox® for both the 8 U/kg group (-6.90; 95% CI: -15.96, 2.16) and the 16 U/kg group (-5.40; 95% CI: -14.46, 3.66).

6.25 The submission stated that the results for the GAS score should be interpreted with care given that GAS was measured in different ways in the trials (investigator in Study 153; family or therapist in Lowe 2006; GAS T scores in Olesch 2010). The submission also noted that the statistically significant differences in favour of Botox® were a consequence of the larger placebo effect in Study 153, where the 'no intervention' arm received 2 U/kg of Dysport® along with a rehabilitation program. The submission claimed that the difference in change from baseline was smaller for Dysport® than for Botox® when compared to no intervention, resulting in an unfair comparison. The

magnitude of any impact on the comparisons is difficult to determine, particularly since patients in Lowe (2006) and Olesch (2010) also received occupational therapy.

***Comparative harms***

- 6.26 The submission provided indirect comparisons of Dysport® and Botox® using grouped adverse events (AEs). The analyses included overall AEs, serious AEs, treatment-related AEs and discontinuations due to AEs, with data from Study 153 for Dysport® sourced from the 16 week timepoint, and for Botox®, week 12 for Fehlings (2018) and week 52 for Olesch (2010). Results are provided in the table below.

Table 10: Results of the indirect comparison of Dysport® and Botox® for safety outcomes

Overall AEs	Dysport® n/N (%)	Common reference no intervention <sup>a</sup> n/N (%)	Botox® n/N (%)	RR (95% CI)
8 U/kg Study 153	40/70 (57.1%)	45/70 (64.3%)	-	0.89 (0.68, 1.16)
16 U/kg Study 153	33/70 (47.1%)	45/70 (64.3%)	-	<b>0.73 (0.54, 0.99)</b>
pooled Dysport® fixed effects (I <sup>2</sup> =0%; p=0.35)				0.82 (0.67, 1.00)
Olesch 2010 (52 weeks)	-	0/11 (0%)	3/11(27.3%)	7.00 (0.40, 121.39)
Fehlings 2018 (12 weeks)	-	33/79 (41.8%)	69/155(44.5%)	1.07 (0.78, 1.46)
pooled Botox® fixed effects (I <sup>2</sup> =0%; p=1)				1.07 (0.78, 1.46)
Indirect pooled Dysport® vs. pooled Botox® (95% CI)				0.77 (0.53, 1.11)
Indirect Dysport® 8 U/kg vs. pooled Botox® (95% CI)				0.57 (0.13, 2.57)
Indirect Dysport® 16 U/kg vs. pooled Botox® (95% CI)				0.47 (0.10, 2.14)
Serious AEs	Dysport® n/N (%)	Common reference no intervention <sup>a</sup> n/N (%)	Botox® n/N (%)	RR (95% CI)
8 U/kg Study 153	3/70 (2.9%)	2/70 (2.9%)	-	0.67 (0.11, 3.87)
16 U/kg Study 153	3/70 (2.9%)	2/70 (2.9%)	-	0.67 (0.11, 3.87)
pooled Dysport® fixed effects (I <sup>2</sup> =0%; p=1)				0.67 (0.19, 2.31)
Fehlings 2018 (12 weeks)	-	1/79 (1.3%)	4/155 (2.6%)	2.04 (0.23, 17.94)
Indirect pooled Dysport® vs. Botox® (95% CI)				0.33 (0.03, 4.00)
Indirect Dysport® 8 U/kg vs. Botox® (95% CI)				0.33 (0.02, 5.36)
Indirect Dysport® 16 U/kg vs. Botox® (95% CI)				0.33 (0.02, 5.36)
Treatment-related AEs	Dysport® n/N (%)	Common reference no intervention <sup>a</sup> n/N (%)	Botox® n/N (%)	RR (95%CI)
8 U/kg Study 153	6/70 (8.6%)	2/70 (2.9%)	-	3.00 (0.63, 14.36)
16 U/kg Study 153	6/70 (8.6%)	2/70 (2.9%)	-	3.00 (0.63, 14.36)
pooled Dysport® fixed effects (I <sup>2</sup> =0%; p=1)				3.00 (0.99, 9.08)
Fehlings 2018 (12 weeks)	-	2/79 (2.5%)	14/155 (9.0%)	3.57 (0.83, 15.31)
Indirect pooled Dysport® vs. Botox® (95% CI)				0.84 (0.13, 5.24)
Indirect Dysport® 8 U/kg vs. Botox® (95% CI)				0.84 (0.10, 7.14)
Indirect Dysport® 16 U/kg vs. Botox® (95% CI)				0.84 (0.10, 7.14)
Discontinuation due to AEs	Dysport® n/N (%)	Common reference no intervention <sup>a</sup> n/N (%)	Botox® n/N (%)	RR (95%CI)
8 U/kg Study 153	0/70 (0%)	2/70 (2.9%)	-	0.20 (0.01, 4.09)
16 U/kg Study 153	0/70 (0%)	2/70 (2.9%)	-	0.20 (0.01, 4.09)
pooled Dysport® fixed effects (I <sup>2</sup> =0%; p=1)				0.20 (0.02, 1.69)
Fehlings 2018 (12 weeks)	-	0/79 (0%)	0/155 (0%)	0.51 (0.01, 25.61)
Indirect pooled Dysport® vs. Botox® (95% CI)				0.39 (0.00, 33.57)
Indirect Dysport® 8 U/kg vs. Botox® (95% CI)				0.39 (0.00, 54.52)
Indirect Dysport® 16 U/kg vs. Botox® (95% CI)				0.39 (0.00, 54.52)

Source: Figure 2-24, p145; Figure 2-25, p146; Figure 2-26, p146 of the submission; Figures 67-69, p83-84 of the ICON report.

AE=adverse event; CI=confidence interval; **bold**=statistically significant

<sup>a</sup> In Study 153 the 2 U/kg Dysport® arm of the trial was used as the 'no intervention' arm

6.27 The submission noted that the occurrence of overall AEs, serious AEs, treatment-related AEs and discontinuation due to AEs was not significantly reduced with Dysport® compared to Botox®. While there were no statistically significant differences between Dysport® and Botox® for the indirect comparisons, many of the comparisons had wide confidence intervals. In addition, many of the comparisons included no

events in one or both arms of a trial. Overall, there was limited comparative evidence to allow for a comprehensive consideration of the comparative safety of Dysport® and Botox® for upper limb spasticity in paediatric patients with cerebral palsy. In its July 2019 consideration of Dysport® for lower limb spasticity in adults following an acute event, the PBAC noted that the ESC considered that Dysport® and Botox® presented similar adverse event profiles, and there were no significant differences between Dysport® and Botox® for any AEs and treatment-emergent AEs (paragraph 6.20, July 2019 Dysport® Public Summary Document (PSD)). The PBAC considered that the claim that Dysport® was non-inferior to Botox® in terms of comparative safety for lower limb spasticity was reasonable (paragraph 6.27, July 2019 Dysport® PSD).

6.28 In addition, the submission did not provide any discussion of what events were included in the grouped AEs used in the indirect comparisons, such as those for treatment-related AEs, and whether these categorisations were the same across the trials. In its discussion of safety outcomes for Study 153 the submission had a summary of individual treatment-emergent AEs, with that table provided below.

**Table 11: Treatment-emergent AEs in Study 153**

AEs n/N (%)	Control group	Treatment groups	
	Dysport® 2 U/kg N=70	Dysport® 8 U/kg N=70	Dysport® 16 U/kg N=70
Any TEAE	45 (64.3%)	40 (57.1%)	33 (47.1%)
Infections and infestations	26 (37.1%)	23 (32.9%)	21 (30.0%)
Upper respiratory tract infection	5 (7.1%)	6 (8.6%)	8 (11.4%)
Viral upper respiratory tract infection	10 (14.3%)	6 (8.6%)	6 (8.6%)
Pharyngitis	6 (8.6%)	3 (4.3%)	4 (5.7%)
Urinary tract infection	0	3 (4.3%)	0
Gastrointestinal disorders	8 (11.4%)	8 (11.4%)	5 (7.1%)
Vomiting	2 (2.9%)	3 (4.3%)	1 (1.4%)
Musculoskeletal and connective tissue disorders	5 (7.1%)	6 (8.6%)	6 (8.6%)
Muscular weakness	1 (1.4%)	3 (4.3%)	4 (5.7%)
Nervous system disorders	3 (4.3%)	7 (10.0%)	4 (5.7%)
Headache	0	4 (5.7%)	2 (2.9%)
Epilepsy	1 (1.4%)	0	3 (4.3%)
Seizure	2 (2.9%)	3 (4.3%)	0
Respiratory, thoracic and mediastinal disorders	3 (4.3%)	7 (10.0%)	3 (4.3%)
Rhinorrhoea	0	5 (7.1%)	1 (1.4%)
Cough	3 (4.3%)	2 (2.9%)	2 (2.9%)
General disorders and administration site conditions	5 (7.1%)	6 (8.6%)	3 (4.3%)
Pyrexia	2 (2.9%)	4 (5.7%)	2 (2.9%)
Injury, poisoning and procedural complications	4 (5.7%)	6 (8.6%)	2 (2.9%)
Fall	3 (4.3%)	2 (2.9%)	1 (1.4%)
Skin and subcutaneous tissue disorders	2 (2.9%)	6 (8.6%)	2 (2.9%)
Rash	0	3 (4.3%)	0

Source: Table 2-62, p116 of the submission.

AEs=adverse events; TEAE=treatment-emergent adverse event

6.29 The submission noted that the most frequently reported AEs were upper respiratory tract infection, and these events are consistent with common respiratory childhood illnesses and other comorbid conditions in paediatric patients with cerebral palsy. This

was reasonable. Remote spread of toxins was identified in the Study 153 as an adverse event of special interest, with the other AE of special interest being hypersensitivity-like reactions. There were no hypersensitivity-like reactions reported. The submission indicated that two patients experienced AEs suggestive of remote spread of toxin effects. The submission stated that there was no evidence of a dose relationship with these events.

### ***Benefits/harms***

6.30 Based on the non-inferiority results presented in the submission, and the indirect treatment comparison, no benefits and harms table has been compiled.

### ***Clinical claim***

6.31 The submission did not use superior, inferior or non-inferior wording as part of its clinical claim, and instead stated that for the treatment of moderate to severe upper limb spasticity in cerebral palsy patients, Dysport® is as effective as Botox® at reducing muscle tone and spasticity and it has a comparable safety profile.

6.32 The evidence presented in the submission partially supports the therapeutic conclusion. While there were generally no statistically significant differences between Dysport® and Botox® for both effectiveness and safety outcomes, those comparisons were limited by a number of issues associated with the indirect comparisons, including small patient numbers in most of the Botox® trials, heterogeneity in many of the comparisons, as well as wide confidence intervals and/or few or no events for many of the safety outcome comparisons.

6.33 In addition, while it was acknowledged by the submission there was no evidence available for the adult population, the submission did not consider the applicability of evidence based on children with a mean age less than 10 years (Study 153) to an adult population.

6.34 The PBAC considered that it was likely that Dysport® was as effective as Botox® at reducing muscle tone and spasticity and had a comparable safety profile.

### ***Economic analysis***

6.35 The submission presented a cost-minimisation analysis based on the indirect comparison versus Botox®.

6.36 The submission indicated that the units used to express the potency of botulinum toxin preparations are not equivalent and therefore not interchangeable on a unit-to-unit basis; and a universal conversion factor between units of Botox® and units of Dysport® has not been determined. This was accurate. Therefore, the submission calculated the equi-effective doses of Dysport® and Botox® using data from Study 153 and from three of the Botox® trials used in the indirect comparisons (Fehlings 2000; Rameckers 2009/Speth 2005; Lowe 2006).

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6.37 The table below provides the calculation of equi-effective doses. Data from the 8 U/kg and 16 U/kg arms from Study 153 for Dysport® were pooled. For the Fehlings (2000) trial, data on mean weight was not available so Australian reference weight was used instead. This was reasonable.

**Table 12: Mean doses in Dysport® and Botox® trials used to calculate equi-effective doses**

	Dysport®	Botox®			
	Study 153	Fehlings 2000	Speth 2005	Lowe et al 2006	Total Botox® trials
Number treated	139	14	10	21	45
Mean weight	32.79	19.30	34.96	19.10	-
Mean dose per arm (U/kg)	11.99	4.08	4.67	7.28	5.70
Mean total dose	394.01	78.74	163.08	139.00	125.61
<b>Equi-effective dose</b>	11.99 (mean dose per arm U/kg) Dysport ÷ 5.70 (weighted mean dose per arm U/kg) <b>2.10 units Dysport® = 1 unit Botox®</b>				

Source: Table 3-2, p162 of the submission; Excel Workbook Ipsen Dysport Paediatric UL Section 3.

6.38 The cost-minimisation analysis is presented below. The submission has proposed ex-manufacturer prices for Dysport 300U and 500U based on approved prices in other indications and which are lower than those calculated in the cost-minimisation. Therefore, the submission has estimated savings based on the assumed equi-effective doses of Dysport® and Botox®.

**Table 13: Results of the cost-minimisation analysis**

	Dysport®	Botox®
Proposed equi-effective dose	2:10U Dysport = 1U Botox	
<b>Treatment cost Botox®</b>		
100U vial AEMP	-	\$337.49
Cost per unit (\$337.49 ÷ 100)	-	\$3.37
<b>Ex-manufacturer prices for Dysport® as per the cost-minimisation analysis</b>		
Cost per unit (\$3.37 ÷ 2.10)	\$1.60	-
300U (\$1.60 × 300U)	\$481.32	
500U (\$1.60 × 500U)	\$802.20	
<b>Proposed ex-manufacturer prices for Dysport® as per the submission</b>		
300U	\$293.64	
500U	\$523.75	
Savings per vial 300U (\$481.32 - \$293.64)	\$187.68	
Savings per vial 500U (\$802.20 - \$523.75)	\$278.45	

Source: Table 3-4, p164 of the submission and the Excel workbook 'Ipsen Dysport Paediatric UL Section 3'.  
AEMP=approved ex-manufacturer price

6.39 While the submission's analysis estimated cost savings, the equi-effective doses based on Study 153 and the selected Botox® trials are not likely to be representative of the actual equi-effective dose, as both Study 153 and the Botox® trials included paediatric patients only. Since the dose used was weight dependent, the calculated equi-effective dose will not apply to adult patients. In addition, the patient numbers in the Botox® trials were small (between 10 and 21 per arm in each trial), indicating that the doses used by those small groups may not be representative of a larger sample.

6.40 Furthermore, in its consideration of Dysport® for lower limb spasticity due to an acute event in July 2019, the PBAC considered that the equi-effective doses of Dysport® and

Botox<sup>®</sup> should be based on the maximum dispensed quantities which would result in equivalent treatment costs per cycle. The PBAC considered that the equi-effective doses were 1500U Dysport<sup>®</sup> was equivalent to 400U Botox<sup>®</sup>, which converts to 3.75U Dysport<sup>®</sup> to 1U Botox<sup>®</sup> (paragraph 7.3, July 2019 Dysport<sup>®</sup> PSD). The PBAC made the same recommendation for Dysport<sup>®</sup> in November 2019 for lower limb spasticity due to acute events other than stroke (paragraph 6.9, November 2019 Dysport<sup>®</sup> PSD) and also for Xeomin<sup>®</sup> for its requested listing for lower limb spasticity due to acute events other than stroke (paragraph 6.10, November 2019 Xeomin<sup>®</sup> PSD). The PBAC noted for its consideration of Xeomin<sup>®</sup> that it had previously considered that the extent to which the potential use of botulinum toxin in both the upper and lower limbs in the same patient would affect utilisation, cost effectiveness and the financial implications remained uncertain. The PBAC was therefore of the view that any pricing arrangement for these indications should take these uncertainties into account by implementing a single price across these conditions (paragraphs 5.9 and 5.10, March 2019 Botox<sup>®</sup> PSD; paragraph 7.17, July 2019 Dysport<sup>®</sup> PSD).

- 6.41 Given the PBAC's recommendation in July 2019, and noting that the cost will relate to the amount dispensed, not the dose injected, the ESC considered that equi-effective doses based on maximum quantities dispensed should be used. For the current requested listing there are two Dysport<sup>®</sup> vials available, 300U with a maximum quantity of 1200U, and 500U with a maximum quantity of 1000U. The submission has assumed that 14.73% of scripts will be for the 300U vial and 85.27% will be for the 500U vial. Applying these proportions to the available maximum quantities results in a maximum quantity of 1029U. The ESC considered that based on the assumed usage of vial sizes, the maximum quantity of Dysport<sup>®</sup> would be 1000U, the Botox<sup>®</sup> maximum quantity would remain at 400U, and the equi-effective doses would be 2.5U Dysport<sup>®</sup> is equivalent to 1U Botox<sup>®</sup>. The submission has provided an option to conduct a sensitivity analysis using this dose equivalence (although the submission did not provide results), as well as a sensitivity analysis using the equi-effective dose based on the maximum quantity for the 500U vial (1200U), which was 3.0:1.
- 6.42 The table below provides the results of the cost-minimisation analysis for the submission's base case, using an equi-effective dose of 2.1:1, along with equi-effective doses based on maximum quantities.

Table 14: Results of the cost-minimisation analysis

Treatment	AEMP	Cost per unit	Dose equivalence	Revised AEMP	Savings per vial compared to current AEMP
<b>Base case:</b> Savings of \$187.68 per vial for the 300U vial and \$278.45 for the 500U vial					
<b>Base case – trial-based doses</b>					
Botox® 100U vial	\$337.49	\$3.37	Dysport® 2.1 units: Botox® 1.0 unit	\$337.49	NA
Dysport® 300U vial	\$293.64	\$1.60 <sup>a</sup>		\$481.32 <sup>b</sup>	\$187.68
Dysport® 500U vial	\$523.75	\$1.60 <sup>a</sup>		\$802.20 <sup>b</sup>	\$278.45
<b>Maximum quantity for Dysport® 500U vial</b>					
Botox® 100U vial	\$337.49	\$3.37	Dysport® 2.5 units: Botox® 1.0 unit	\$337.49	NA
Dysport® 300U vial	\$293.64	\$1.35 <sup>a</sup>		\$404.99	\$111.35
Dysport® 500U vial	\$523.75	\$1.35 <sup>a</sup>		\$674.98	\$151.23
<b>Maximum quantity for Dysport® 300U vial</b>					
Botox® 100U vial	\$337.49	\$3.37	Dysport® 3.0 units: Botox® 1.0 unit	\$337.49	NA
Dysport® 300U vial	\$293.64	\$1.12 <sup>a</sup>		\$337.49	\$43.85
Dysport® 500U vial	\$523.75	\$1.12 <sup>a</sup>		\$562.48	\$38.73

Source: Table 3-4, p164; Table 3-6, p165; Table 3-7, p166 of the submission and the Excel workbook 'Ipsen Dysport Paediatric UL Section 3'.

<sup>a</sup> Calculated as Botox® cost per unit multiplied by dose equivalence.

<sup>b</sup> Calculated as cost per unit multiplied by number of units, with rounding.

6.43 The submission noted that all scenarios resulted in cost-savings per vial for Dysport®. The estimated cost savings per vial were considerably less when the equi-effective doses based on the maximum quantities were used, compared to the submission's base case estimates.

### **Drug cost/patient/course**

6.44 The submission assumed, based on PBS item data for use of Dysport® between 2017 and 2019, that utilisation would be split between the 300U and 500U vial sizes at a ratio of 14.73% to 85.27%. Applying these proportions to the requested price of each vial results in a drug cost, based on the maximum quantities of each vial size, of \$1,113.61 per cycle.

### **Estimated PBS usage & financial implications**

6.45 This submission was not considered by DUSC. The submission applied a market share approach to estimate the number of Dysport® scripts that will be used for treatment of upper limb spasticity due to cerebral palsy. The table below summarises the inputs used for the financial estimates.

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Table 15: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Proportion of Botox® scripts applicable to listing	DUSC 2018 report: 63.45%, calculated using 2 years of PBS data for Botox® for upper limb spasticity due to CP and stroke.	While the proportion is likely to be reasonable, the financial estimates were sensitive to the calculated proportion.
Market growth rate	Calculated from the DUSC 2018 report: 16.22%, based on MBS data from 2011 to 2017.	May not be accurate as the extrapolation was based on MBS data, which DUSC indicated differed from PBS data for use of BoNT-A in spasticity (p17 2018 DUSC report).
Uptake rate	Sponsor assumption: 50% in Years 1 to 6.	While 50% uptake splits the market between Dysport® and Botox®, there was no evidence or discussion provided around why a 50% rate was chosen. Nor was a rationale provided for assumption of the same rate across the first 6 years of listing. The ESC considered that a market share estimate of 50% was highly optimistic.
Split of Dysport® vial size usage	PBS item reports for Dysport® use between 2017 and 2019: 300U 14.73%; 500U 85.27%	The split was based on Dysport® usage for all conditions, which may not reflect usage under the proposed listing. However the estimates did not show much sensitivity to this component.
Offsets for Botox®	Cost offsets for Botox® were based on equi-effective doses and the assumed uptake rate.	The estimated offsets are not likely to be accurate, given issues with the equi-effective dose and assumption of a 50% uptake rate.
MBS items	Not included.	Not appropriate, as MBS items are used by both Dysport® and Botox® patients and may be used with a different frequency by Dysport® patients.

Source: Section 4.1 to Section 4.5, p168-175 of the submission.

6.46 The estimated script numbers and costs of the PBS listing of Dysport® are provided below. The submission did not include discussion or estimates of patient numbers, and instead applied the market share approach to estimation of script numbers only.

Table 16: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of scripts dispensed <sup>a</sup>	■	■	■	■	■	■
<b>Estimated financial implications of Dysport®</b>						
Cost to PBS/RPBS <sup>b</sup>	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Copayments <sup>b</sup>	-\$ ■	-\$ ■	-\$ ■	-\$ ■	-\$ ■	-\$ ■
Cost to PBS/RPBS less copayments	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Cost offsets for substituted Botox®	-\$ ■	-\$ ■	-\$ ■	-\$ ■	-\$ ■	-\$ ■
<b>Net financial implications</b>						
<b>Net cost to PBS/RPBS</b>	<b>-\$ ■</b>	<b>-\$ ■</b>	<b>-\$ ■</b>	<b>-\$ ■</b>	<b>-\$ ■</b>	<b>-\$ ■</b>

Source: Table 4-9, p172; Table 4-11, p172 of the submission.

<sup>a</sup> The submission assumed there would be 3.26 Dysport® prescriptions per year based on a 16 week treatment cycle, and this was converted to a relative re-treatment (0.75) based on the 12 week treatment cycle for Botox®. Therefore, the submission used 2.44 treatments per year to calculate scripts that would substitute for Botox®.

<sup>b</sup> The submission did not provide total PBS/RPBS costs or patient copayments, however these could be calculated in the submission's Section 4 Excel workbook and that was done during the evaluation.

6.47 There was a net cost saving to the PBS/RPBS in Year 6 and over the first 6 years of listing. The estimated savings are largely based on the equi-effective dose of 2.1:1

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used by the submission, the assumed uptake rate of 50% across the first 6 years of listing and the estimated market growth of 16.22%.

- 6.48 The PSCR noted that the assumption in the submission that there would be 16 weeks between Dysport® treatments was conservative as the majority of patients in Study 153 were retreated between 16 and 28 weeks. In addition, the Product Information for Botox® indicated that the minimum time between treatments is 12 weeks, with the potential difference, if Dysport® was recommended, likely resulting in cost savings to the PBS/RPBS. The ESC considered that in practice the dosing interval may relate more to the timing of scheduled review than to the pharmacology of the drugs.
- 6.49 As the submission did not include MBS costs for administration of Dysport® or Botox®, the values presented by the submission did not accurately estimate the financial impact of the requested PBS listing of Dysport®. Omission of MBS costs would have underestimated costs. The PSCR stated that given the potential differences between treatment durations, it is likely that Dysport® will result in fewer MBS items being processed.
- 6.50 The PBAC had stated for the recommendation of Dysport® in July 2019 that equi-effective doses assuming maximum quantity should be used (paragraph 7.3, July 2019 Dysport® PSD). Applying maximum quantity to equi-effective doses for the current submission results in a dose equivalence of 2.5:1. Use of this dose equivalence decreased the estimated net savings over the first 6 years of listing. The impact of alteration of financial estimate inputs on the estimated net savings over the first 6 years of listing are provided below.

Table 17: Sensitivity analyses – impact on estimated savings

Sensitivity analysis	Net savings over first 6 years of listing (base case \$ [REDACTED])
Dose equivalence 2.5:1	\$ [REDACTED] M
Dose equivalence 3.0:1	\$ [REDACTED] M
Proportion of Botox® scripts applicable 50%	\$ [REDACTED] M
Proportion of Botox® scripts applicable 75%	\$ [REDACTED] M
Vial split 300U 50%; 500U 50%	\$ [REDACTED] M
Market share 60% for first 6 years	\$ [REDACTED] M
Market growth 10%	\$ [REDACTED] M
Dose equivalence 2.5:1 and market share 40%	\$ [REDACTED] M
Dose equivalence 2.5:1 and market growth 10%	\$ [REDACTED] M

Source: Excel workbook 'Ipsen Dysport Paediatric UL Section 4'.

- 6.51 Increasing the market share to 60% increases estimated net savings, but when market share was decreased and dose equivalence altered to 2.5:1, the estimated net savings decreased. When market growth was decreased from the submission's estimate of 16.22% to 10%, estimated net savings over the first 6 years of listing decreased. When dose equivalence was changed to 2.5:1 and market growth decreased to 10%, the estimated savings also decreased. The PSCR noted that all analyses resulted in a cost saving.

- 6.52 Overall, the equi-effective doses have considerable impact on the estimates, and following the recommendation of the PBAC in July 2019 for dose equivalence based on maximum quantities, the submission's estimates should be lower by about 50%. There was considerable uncertainty around the financial estimates given the dose equivalence used, the assumed market share, the estimated market growth, and omission of MBS costs.

### **Financial Management – Risk Sharing Arrangements**

- 6.53 The submission stated that no risk-sharing arrangements (RSA) are proposed for this requested listing. There is a RSA for upper limb spasticity due to stroke or acute events. The sponsor did not provide discussion of why an RSA was not proposed. Given the uncertainty around the estimated financial implications of PBS listing for Dysport<sup>®</sup>, an RSA may be appropriate. The pre-PBAC response noted that as all scenarios for the listing of Dysport were cost saving and as the patient population is well established, it was not appropriate to establish a RSA with this potential listing.

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

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the listing of clostridium botulinum toxin (Dysport<sup>®</sup>), on the basis that it should be available only under special arrangements under Section 100 (Botulinum Toxin Program), for the treatment of moderate to severe focal spasticity of the upper limb in patients with cerebral palsy.
- 7.2 The PBAC was satisfied that Dysport<sup>®</sup> was non inferior to botulinum toxin type A (Botox<sup>®</sup>) in terms of comparative efficacy and safety.
- 7.3 The PBAC considered that the Dysport<sup>®</sup> restriction should be consistent with the current Botox<sup>®</sup> restrictions for moderate to severe focal spasticity of the upper limb in patients with cerebral palsy.
- 7.4 The PBAC considered that Botox<sup>®</sup> was the appropriate comparator.
- 7.5 The PBAC noted that the submission was based on indirect comparisons between one Dysport<sup>®</sup> trial (Study 153) and five Botox<sup>®</sup> trials (Fehlings 2018; Fehlings 2000; Rameckers 2009/Speth 2005; Lowe 2006; Olesch 2010). The PBAC noted that Study 153 was a randomised, double-blind comparison of three Dysport doses (2 U/kg, 8 U/kg and 16 U/kg) and did not have a placebo or 'no intervention' arm. The PBAC noted that the submission used the 2 U/kg arm as the no intervention arm, which was considered to be appropriate.
- 7.6 The PBAC noted that the Dysport<sup>®</sup> and Botox<sup>®</sup> trials were conducted in the paediatric population. The PBAC agreed with the ESC in considering that, provided fixed contractures had not developed, there would be no clinical reason to expect a lack of effectiveness in adults and noting that, given the nature of the therapy, treatment was unlikely to be continued if no effect was observed.

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- 7.7 The PBAC noted that the indirect comparisons were limited due to a number of issues, including small patient numbers in most of the Botox trials, heterogeneity in many of the comparisons, and wide confidence intervals and/or few or no events for many of the safety comparisons. However, overall, the PBAC considered that the evidence suggested that Dysport® was likely to be non-inferior to Botox® in terms of efficacy and safety.
- 7.8 The PBAC noted that the submission presented a cost minimisation analysis between Dysport® and Botox® based on an equi-effective dose derived from Study 153 for Dysport® (the 8 U/kg and 16 U/kg data were pooled) and three of the Botox® trials (Fehlings 2000, Rameckets 2009/Speth 2005, and Lowe 2006). The PBAC noted that the nominated equi-effective doses (2.1 U Dysport® was equivalent to 1.0 U Botox®) may not have been representative of the actual equi-effective doses as the trials only included paediatric patients.
- 7.9 Furthermore, in its consideration of Dysport® for lower limb spasticity due to an acute event in July 2019, the PBAC considered that the equi-effective doses of Dysport® and Botox® should be based on the maximum dispensed quantities which would result in equivalent treatment costs per cycle (paragraph 7.3, July 2019 Dysport® PSD).
- 7.10 The PBAC considered that equi-effective doses based on maximum quantities dispensed should be used. The PBAC considered that the maximum quantity of Dysport® would be 1000 U and the maximum quantity of Botox® would be 400 U, resulting in an equi-effective dose of:
- $$2.5 \text{ U Dysport}^{\circledR} = 1 \text{ U Botox}^{\circledR}$$
- 7.11 The PBAC considered that the assumed 50% uptake of Dysport® was overestimated, but noted that the financial implication estimates for listing Dysport® on the PBS were cost saving for all presented analyses.
- 7.12 The PBAC noted that supportive advice from the Medical Services Advisory Committee (MSAC) was foreshadowed to request changes to the item descriptor of MBS item 18361, to include 'Clostridium Botulinum Type A Toxin-Haemagglutinin Complex (Dysport)' in the list of botulinum toxins associated with the item, as well as minor amendments to align the descriptor with the current PBS listing.
- 7.13 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because Dysport® is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over Botox®, and not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.
- 7.14 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## 8 Recommended listing

8.1 Amend existing listing as follows:

*Add indication (9102 – moderate to severe spasticity of the upper limb) as follows:*

Name, restriction, manner of administration, form	Max. Qty (packs)	Max. Qty (units)	No. of repeats	Proprietary name and manufacturer
CLOSTRIDIUM BOTULINUM TYPE A TOXIN-HAEMAGGLUTININ COMPLEX clostridium botulinum type A toxin-haemagglutinin complex 300 units injection, 1 vial	4	4	0	Dysport® Ipsen Pty Ltd
clostridium botulinum type A toxin-haemagglutinin complex 500 units injection, 1 vial	2	2	0	

**Restriction Summary 8821 / ToC: 5178 (reverse/undo sponsor proposed changes back to original details):**

<b>Concept ID</b>	<b>Category / Program:</b> Section 100 – Botulinum Toxin Program
	<b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
	<b>Restriction Type/ Method:</b> <input checked="" type="checkbox"/> Authority Required – Streamlined (5178)
	<b>Episodicity:</b> [nil]
	<b>Severity:</b> Moderate to severe
	<b>Condition:-</b> spasticity of the upper limb
9102	<b>PBS Indication:</b> Moderate to severe spasticity of the upper limb
9104	<b>Clinical criteria:</b>
9103	Patient must have cerebral palsy
	<b>Population criteria:</b>
	Patient must be aged from 2 to 17 years inclusive; <del>or</del>
15241	<b>Treatment criteria:</b>
8656	Must be treated by a neurologist; or
15213	Must be treated by an orthopaedic surgeon; or
10064	Must be treated by a paediatrician; or
15214	Must be treated by a rehabilitation specialist; or
15196	Must be treated by a plastic surgeon
15277	<b>Cautions:</b> Contraindications to treatment include known sensitivity to botulinum toxin
9806	<b>Administrative Advice:</b> The units used to express the potency of botulinum toxin preparations currently available for PBS subsidy are not equivalent

**Restriction Summary 8928 / ToC: 8929 edited:**

<b>Concept ID</b>	<b>Category / Program:</b> Section 100 – Botulinum Toxin Program
	<b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
	<b>Restriction Type / Method:</b> <input checked="" type="checkbox"/> Authority Required – Streamlined (8929)
9102	<b>PBS Indication:</b> Moderate to severe spasticity of the upper limb
9104	<b>Clinical criteria:</b>
9103	Patient must have cerebral palsy
8384	<b>Population criteria:</b>
8383	Patient must be aged 18 years or older
15241 15273	<b>Treatment criteria:</b>
8656	Must be treated by a neurologist; or
15213	Must be treated by an orthopaedic surgeon; or

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10064	Must be treated by a paediatrician; or
15214	Must be treated by a rehabilitation specialist; or
15196	Must be treated by a plastic surgeon; or
15277	<b>Cautions:</b> Contraindications to treatment include known sensitivity to botulinum toxin
9806	<b>Administrative Advice:</b> The units used to express the potency of botulinum toxin preparations currently available for PBS subsidy are not equivalent

***This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.***

## **9 Context for Decision**

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

## **10 Sponsor's Comment**

The sponsor had no comment.