7.02 BOTULINUM TOXIN TYPE A PURIFIED NEUROTOXIN COMPLEX, Lyophilised powder for injection, 100 units, Botox®, Allergan Australia

1 Purpose of Application

1.1 The resubmission requested a Section 100 Authority Required listing for botulinum toxin type A (BOTOX®) for treatment of adult patients with moderate to severe lower limb focal spasticity following a stroke. BOTOX® is currently listed on the PBS for the treatment of adult patients with moderate to severe spasticity of the upper limb following a stroke. A previous submission to the PBAC for lower limb spasticity following stroke was rejected due to uncertain clinical benefit and high and uncertain cost-effectiveness in July 2008.

1.2 At the November meeting, the PBAC also considered submissions for Clostridium botulinum type A toxin-haemagglutinin complex (Dysport®) for the treatment of focal spasticity following an acute event in the lower limb (Item 6.02) and the upper limb (6.03).

1.3 Listing was requested on the basis of a cost-utility analysis versus placebo. The key components of the clinical issue are presented in Table 1.

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

Component	Description
Population	Adult patients with LLFS following stroke
Intervention	BOTOX® (Botulinum toxin type A, up to 400U)
Comparator	Placebo/Standard management
Outcomes	In the main trial (REFLEX) whose results were relied in the economic evaluation: Primary outcome: Modified Ashworth Scale (MAS) Secondary outcomes: Goal Attainment Scale (GAS), Clinical Global Impression (CGI)
Clinical claim	In adults with lower limb focal spasticity, BOTOX® as an adjunctive treatment to standard management is more effective than placebo (standard management alone) at reducing the severity of spasticity and improves progress towards treatment goals. The safety profile of BOTOX® with standard management is non-inferior to placebo (standard management alone).

Source: Table 1.1-1, p2 of the submission.

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

2 Requested listing

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

2.2 The submission did not propose a grandfathering restriction. The Secretariat drafted a grandfathering restriction based on the restriction proposed by the submission.

Name, Restriction, Manner of administration and form	Max. Qty. (units)	№. of Rpts	Dispensed Price for Max. Quantity	Proprietary Name and Manufacturer	
BOTULINUM TOXIN TYPE A 100 units injection, 1 vial	4	0	Public:$1349.96 Private: $1397.25	Botox®	Allergan

Category / Program :	Section 100 – Botulinum Toxin Program
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity	Moderate to severe
Condition: **Treatment phase**	Lower limb spasticity following a stroke *Initial and continuing treatment*
PBS Indication:	Moderate to severe spasticity of the lower limb following a stroke
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 stroke, defined as a Modified Ashworth Scale rating of 3 or more, **AND** The treatment must only be used as second line therapy when standard management has failed; OR The treatment must only be used as an adjunct to physical therapy, **AND** The treatment must not continue if the patient does not respond (defined as not having had a decrease in spasticity rating of a least 1, using the Modified Ashworth Scale, in at least one joint) after two treatment periods *per lower limb,* **AND** Patient must not have established severe contracture in the limb to be treated.
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 of the stroke 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 400U every 12 weeks.*~~
Administrative Note	*The units used to express the potency of botulinum toxin preparations currently available for PBS subsidy are not equivalent.*
Caution	*Contraindications to treatment include known sensitivity to botulinum toxin.*

Grandfathering restriction:

Category / Program :	Section 100 – Botulinum Toxin Program
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity **Condition:**	Moderate to severe Lower limb spasticity following a stroke
PBS Indication: **Treatment phase:** **Restriction Level / Method:**	Moderate to severe spasticity of the lower limb following a stroke *Initial and continuing treatment – grandfathered patients* ☐Restricted benefit ☐Authority Required - In Writing

Clinical criteria:	☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined ~~The condition must be moderate to severe spasticity of the lower limb/s following stroke, defined as a Modified Ashworth Scale rating of 3 or more,~~ ~~**AND**~~ The treatment must only be used as second line therapy when standard management has failed; OR The treatment must only be used as an adjunct to physical therapy, **AND** The treatment must not continue if the patient does not respond (defined as not having had a decrease in spasticity rating of at least 1, using the Modified Ashworth Scale, in at least one joint) after two treatment periods *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 of the stroke 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 400U every 12 weeks.*~~
Administrative Note	*The units used to express the potency of botulinum toxin preparations currently available for PBS subsidy are not equivalent.*
Caution	*Contraindications to treatment include known sensitivity to botulinum toxin.*

2.3 The requested restriction wording was similar to the listing of BOTOX® in upper limb spasticity following stroke, except:

- The removal of the life time limit of four treatment periods (total BOTOX®, Dysport®, Xeomin®) per limb. The resubmission argued removal of this criterion was necessary given that the condition is chronic in nature. This was supported by the Rehabilitation Medicine Society of Australian and New Zealand (RMSANZ). The PBAC agreed that the removal of a lifetime limit of four treatments was consistent with clinical practice for continuing responders. The PBAC noted expert opinion which indicated that reinjection intervals increase with continued treatment and considered that a limit of four treatment periods per lower limb in the first year, with a limit of two treatment periods per lower limb per year from Year 2 might be reasonable.
- The proposed restriction omitted the criterion: "the treatment must not be initiated until three months post-stroke". The resubmission indicated this was consistent with recent clinical evidence that supports early intervention to maximise patient outcomes. This was supported by the RMSANZ. 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.

- In the submission, the continuing statement read "The treatment must not continue if the patient does not respond (defined as not having had a decrease in spasticity rating of greater than 1, using the Modified Ashworth Scale (MAS), in at least one joint) after two treatment periods per lower limb." This was consistent with the current PBS listing for upper limb spasticity following a stroke. The sponsor clarified in the PSCR that the continuing criterion should require an improvement of "at least 1" to align the listing with the November 2007 Public Summary Document (PSD) for Dysport® that stated "botulinum treatment resulted in a large number of patients with a decrease in MAS of at least 1 point in at least joint at week 20 and agreed that this change was significant."

2.4 The PBAC considered that an improvement of at least 1 MAS point, when accompanied with other functional improvements, was reflective of the trial-defined response outcome and likely to reflect a patient relevant response in some patients.

2.5 The PBAC considered that to ensure consistency between the current upper limb focal spasticity restriction and the trial evidence presented for lower limb spasticity additional clinical opinion would be useful regarding the continuation criteria.

2.6 The PBAC noted that maximal response to treatment occurs in the evidence at about four to eight weeks following injection with botulinum toxin type A, and that response would ideally be assessed within this time frame.

- The Secretariat proposed a maximum dose per patient of 400U every 12 weeks be included in the restriction. The PSCR requested that this condition be removed to grant physicians flexibility in treatment scheduling. The PSCR contended that there is currently no maximum dose specified for the cerebral palsy item codes, which permits the dispensing of two scripts on the same day. This is stated to reduce administrative burden and possible treatment disruption. The PBAC considered that the limited number of treatments per year removed the need for a minimum treatment interval.

2.7 Based on the populations in the primary clinical evidence, the proposed restriction was for moderate to severe lower limb focal spasticity in post-stroke patients. This was narrower than the TGA indication for BOTOX®, which is for focal spasticity of any severity, aetiology and at any affected location(s). Following a submission by RMSANZ to the PBAC in July 2018 to broaden PBS coverage to include any aetiology of moderate to severe focal spasticity, the sponsor proposed an alternative listing which included patients with lower limb focal spasticity from traumatic brain injury, spinal cord injury and other acute aetiologies – see paragraph 6.9.

2.8 The submission requested a grandfathering provision for patients who have been accessing BOTOX® for non-PBS indications reimbursed by a public hospital, private health insurance company or purchased by the patient.

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

3 Background

Registration status

3.1 BOTOX® was TGA registered on August 2003 for the treatment of focal spasticity in adults.

3.2 Other approved therapeutic indications include overactive bladder, urinary incontinence, chronic migraine, strabismus, blepharospasm, cervical dystonia (spasmodic torticollis), dynamic equinus foot deformity due to cerebral palsy in patients two years and older, severe primary hyperhidrosis of the axillae, and spasmodic dysphonia.

Previous PBAC consideration

3.3 The PBAC previously considered four major submissions and one minor submission requesting the PBS listing of BOTOX® treatment for focal spasticity. In July 2008 the PBAC considered a submission for the treatment of lower limb focal spasticity post-stroke.

3.4 In May 2018, DUSC provided advice to the PBAC in a review of utilisation of botulinum toxin supplied through the PBS for treatment of spasticity in patients with cerebral palsy or following a stroke, and for spasmodic torticollis, blepharospasm and hemifacial spasm. 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.

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

4 Population and disease

4.1 Spasticity of the lower limbs typically affects the foot, knee and hip; with examples including equinovarus foot, valgus foot, striatal toe, stiff knee, flexed knee, adducted thighs, and flexed hip. Lower limb focal spasticity can be very disabling, with muscle stiffness, pain and loss of joint range impairing motor performance, activities of daily living and degree of independence.

4.2 BOTOX® is a neuromuscular blocking agent that inhibits peripheral acetylcholine release at nerve fibres that stimulate muscle contraction. This results in reduced muscle tone and improvement in spasticity severity.

4.3 The dose administered, 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 resubmission stated that the maximum dose must not exceed 400U in a single

injection session[1]. If treatment is required for both upper and lower limbs, the total dose also must not exceed 400U. This maximum dose was not reported in the approved BOTOX® Product Information.

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 resubmission indicated that the availability of BOTOX® on the PBS will not alter the current management algorithm, but rather a provision of Government-funded treatment for all patients will ensure equity of access.

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

5 Comparator

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

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician discussed the use of botulinum toxin type A in clinical practice, and clarified the goals of treatment, which included improving comfort, facilitating personal care, decreasing the burden on carers and increasing functional independence for patients. The clinician described the use of botulinum toxin type A as treatment which is adjuvant to physical therapies including stretching and training of antagonist muscles. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating spasticity of the lower limb.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (3), health care professionals (9) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with BOTOX®, as part of broader management plan, including improved mobility, reduction of pain, improved quality of life and a reduction in the burden of care.

6.3 The PBAC noted the advice received from Stroke Recovery Association, NSW

[1] Olver, J., Esquenazi, A. & Fung, V. S., 2010. Botulinum toxin assessment, intervention and aftercare for lower limb disorders of movement and muscle tone in adults: International consensus statement. European Journal of Neurology, 17(Suppl. 2), p. 57–73.

endorsing the use of BOTOX® as part of a rehabilitation program for lower limb spasticity to improve mobility, reduce pain and potentially avoid costly surgery. The PBAC noted that this advice was supportive of the BOTOX® in the submission.

Clinical trials

6.4 The resubmission was based on:

i) two primary direct comparative randomised controlled trials comparing BOTOX® to placebo, REFLEX and Trial 512, enrolling post stroke patients with lower limb focal spasticity and meeting the proposed PBS criteria of baseline MAS score ≥3,

ii) seven secondary randomised trials enrolling post-stroke patients with lower limb spasticity, but with lower baseline MAS scores, and

iii) seven supportive trials enrolling patients with lower limb spasticity due to other aetiologies.

Of the included trials, four secondary trials (Trials 702, 030, 138, 501/502) and one supportive trial (Verplancke 2005) had previously been considered by the PBAC.

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

Table 3: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
Primary trials		
REFLEX	BOTOX® treatment in adult patients with post-stroke lower limb spasticity. Interim Report (double blind phase). Study	September 2014.
	BOTOX® treatment in adult patients with post-stroke lower limb spasticity. Final Report	July 2015
	Wein T, Esquenazi A, Jost WH, Ward AB, Pan G, Dimitrova R. OnabotulinumtoxinA for the treatment of post-stroke distal lower-limb spasticity: a randomized trial.	*PM R.* 2018 Jul 10(7):693-703.
	A Multicenter Study to Evaluate the Efficacy and Safety in Patients with Post-Stroke Lower Limb Spasticity Receiving a Double-Blind, Placebo-Controlled GSK1358820 Treatment Followed by an Open-Label GSK1358820 Treatment.	June 2009
Trial 512	Kaji R, Osako Y, Suyama K, et al. 2010. Botulinum toxin type A in post-stroke lower limb spasticity: a multicenter, double-blind, placebo-controlled trial.	J Neurol. 257(8):1330-1337.
	Kimura, A., et al. 2010. Efficacy and safety of Botulinum Toxin Type A in treating lower limb spasticity in post stroke patients: a multicentre, double-blind, placebo controlled trial followed by an open-label trial. [Full Length Text Not Used, in Japanese].	Japanese journal of rehabilitation medicine 47, 626-636
Secondary trials		
Trial 702	A two-part multicenter study of BOTOX® (botulinum toxin type A) in the treatment of lower limb spasticity during stroke rehabilitation (Part I—double-blind, placebo-controlled, parallel, randomised, & Part II—open-label follow-up).	July 2002
	Dunne JW, Gracies JM, Hayes M, et al. 2012. A prospective, multicenter, randomized, double-blind, placebo-controlled trial of onabotulinumtoxinA to treat planter flexor/invertor overactivity after stroke.	Clin Rehab. 26(9):787-797.
	A Multicentre, Double-blind, Prospective, Randomised, European and Canadian Study to Evaluate Patient Outcomes and Costs of Managing Adults with Spasticity and Associated Focal Spasticity	August 2011

Trial ID	Protocol title/ Publication title	Publication citation
BEST	Borg J, Ward AB, Wissel J, et al. 2011. Rationale and design of a multicentre, double-blind, prospective, randomized, European and Canadian study: evaluating patient outcomes and costs of managing adults with post-stroke focal spasticity.	Journal of rehabilitation medicine 43(1):15-22.
	Ward AB, Wissel J, Borg J, et al. 2014. Functional goal achievement in post-stroke spasticity patients: the BOTOX® Economic Spasticity Trial (BEST).	Journal of rehabilitation medicine 46(6):504-13.
Trial 030	A multicenter, double-blind, placebo-controlled, parallel group study of pulmonary function safety of BOTOX® (botulinum toxin type A) purified neurotoxin complex for the treatment of focal spasticity post stroke.	February 2002
Trial 138/139	A randomised, double-blind, placebo-controlled, clinical trial to evaluate the safety, efficacy and dosing of BOTOX® (botulinum toxin type A) purified neurotoxin complex for the treatment of lower limb spasticity in post-stroke patients	August 2001
Trial 501/502	A multicenter, randomised, double-blind, placebo-controlled clinical trial to evaluate the safety, dosing, and efficacy of a single dose of BOTOX® (botulinum toxin type A) purified neurotoxin complex for the management of lower limb spasticity after stroke.	February 2001
	A multicenter, randomised, double-blind, placebo-controlled clinical trial to evaluate the safety, dosing, and efficacy of BOTOX® (botulinum toxin type A) purified neurotoxin complex for the management of lower limb spasticity after stroke.	April 2001
Picelli 2014	Picelli A, Dambruoso F, Bronzato M, et al. 2014. Efficacy of therapeutic ultrasound and transcutaneous electrical nerve stimulation compared with botulinum toxin type A in the treatment of spastic equinus in adults with chronic stroke: a pilot randomized controlled trial	Top Stroke Rehabil. 2014;21 Suppl 1:S8-16.
Tao 2015	Tao, W, Yan D, Li J-H, Shi Z-H. 2015. Gait improvement by low-dose botulinum toxin A injection treatment of the lower limbs in subacute stroke patients	J Phys Ther Sci 27(3): 759-762.
Supplementary trials (other aetiologies)		
Fietzek 2014	Fietzek UM, Kossmehl P, Schelosky L, et al. 2014. Early botulinum toxin treatment for spastic pes equinovarus - a randomized double-blind placebo-controlled study	European Journal of Neurology 21(8):1089-1095
Grazko 1995	Grazko MA, Polo KB, Jabbari B. 1995. Botulinum toxin A for spasticity, muscle spasms, and rigidity. Neurology 45(4):712-717.	Neurology 45(4):712-717.
Lannin 2018	Lannin NA, ADA L, Levy T, et al. Intensive therapy after botulinum toxin in adults with spasticity after stroke versus botulinum toxin alone or therapy alone: a pilot, feasibility randomized trial.	Pilot and Feasibility Studies (2018) 4:82
Maanum 2011	Maanum G, Jahnsen R, Stanghelle JK, et al. 2011a. Effects of botulinum toxin A in ambulant adults with spastic cerebral palsy: a randomized double-blind placebo controlled-trial.	Journal of rehabilitation medicine 43(4):338-347.
Richardson 2000	Richardson D, Sheean G, Werring D, et al. 2000. Evaluating the role of botulinum toxin in the management of focal hypertonia in adults.	Journal of Neurology, Neurosurgery, and Psychiatry 69(4):499-506.
Snow 1990	Snow BJ, Tsui JKC, Bhatt MH, et al. 1990. Treatment of spasticity with botulinum toxin: A double-blind study.	Annals of Neurology 28(4):512-515
Verplancke 2005	Verplancke D, Snape S, Salisbury CF, Jones PW and Ward AB. 2005. A randomized controlled trial of botulinum toxin on lower limb spasticity following acute acquired severe brain injury.	Clinical Rehabilitation 19:117-25.

Source: Table 8 – Primary BOTOX® RCT Search, Literature Search Report, Appendix 7 of the resubmission

6.6 The resubmission's clinical claims for efficacy and safety were based on the primary evidence and were supported by the secondary evidence. A claim of superior efficacy versus placebo was based on the outcomes: i) mean change in MAS; and ii) proportion of patients with a one-point improvement in MAS (responders); and supported by iii)

improvements in clinician-rated global assessments. A claim of non-inferior safety was based on a comparison of adverse event categories and individual adverse events in the trials. The modelled economic evaluation was based on individual patient data from REFLEX.

6.7 One secondary trial identified by the resubmission, Picelli 2014, compared BOTOX® to transcutaneous electrical nerve stimulation (TENS) and therapeutic ultrasound (US), unlike other included trials that compared BOTOX® to placebo injections. As TENS and US are not routinely used in Australia to manage lower limb focal spasticity, results of Picelli 2014 were not considered in the evaluation.

6.8 A proportion of patients in the secondary trials matched the proposed PBS criteria (baseline MAS ≥3), and their results are referenced alongside the primary trials.

6.9 The submission contained supplementary evidence for patients with lower limb spasticity due to aetiologies other than stroke; however, this was broader than the requested restriction. The evidence indicated that BOTOX® treatment reduced the severity of spasticity, patient-rated muscle-stiffness/spasticity during walking, painful muscle spasms and improved hygiene. However, the studies were low quality, were very heterogeneous, suffered from methodological issues including small sample sizes, and often failed to report a difference between BOTOX® and standard treatment. Overall, it was unclear if BOTOX® led to significant improvements compared to placebo in aetiologies other than stroke.

6.10 Acknowledging Dysport® as a near market comparator, the resubmission also presented evidence for Dysport® from five trials identified from the literature. A side by side comparison of data from the main trials for BOTOX® (REFLEX, Trials 512) and Gracies 2017 for Dysport® was presented. Although MAS results appeared similar, the resubmission did not provide formal statistical comparisons of BOTOX® and Dysport®.

6.11 The key features of the included primary and secondary trials are summarised in Table 4.

Table 4: Key study characteristics of the included primary and secondary trials (excluding Picelli 2014)

Trial/country of conduct	N	Patient population	Design/duration	Muscles injected	Concomitant physical therapy	Key Outcomes	Risk of bias
Primary trials: BOTOX® versus PBO							
REFLEX (Wein 2018) Multi-country	468	Spastic equinus or equinovarus post stroke (≥6mth prior), MAS ≥3	P3,R; 1 cycle (12-weeks), DB; 3 cycles (up to 60 weeks) OL	• Mandatory: Ankle plantar flexors • Optional: dorsiflexors, rectus femoris, hamstrings	Physiotherapy: [redacted]% BOTOX®, [redacted]% PBO	• 1^0: MAS wk4-6 • 2^0: CGI, GAS, Pain score while walking, gait speed; MAS (optional muscles) wk6	Low
Trial 512 [b] (Kaji 2010) Japan	120	Spastic equinus post stroke (≥6mth prior), MAS ≥3	P3,R; 1 cycle (12-weeks), DB; 3 cycles (48-weeks) OL	Ankle plantar flexors	Any rehabilitation: 58.6% BOTOX®, 53.2% PBO	• 1^0: MAS • 2^0: CGI, gait speed; physician rating scale	Low

Trial/country of conduct	N	Patient population	Design/duration	Muscles injected	Concomitant physical therapy	Key Outcomes	Risk of bias
Secondary trials: BOTOX® versus PBO							
Trial 702 (Dune 2012) Australia	85	Spastic equinovarus post stroke (≥6wks prior), AS ≥2	P3,R; 1 cycle (16-weeks), DB; 1 cycle (12-weeks) OL	Posterior tibialis, soleus, and either the flexor digitorum longus or the medial gastrocnemius	Physiotherapy: 34.6% BOTOX® 200U, 39.3% BOTOX® 300U, 50% PBO	• 1^0: AS	Low
Trial 030 Multi-country	108	Upper and/or LLFS post stroke (≥6 weeks prior); AS ≥2.	P2, R; 2 cycles (24 wks)	Extensor hallucis longus, Flexor digitorum brevis and longus, Flexor hallucis longus, gastrocnemius, iliacus, hamstrings, quadriceps, rectus femoris, soleus, tibialis anterior, tibialis posterior	NR	• 1^0: Pulmonary function tests • 2^0: AS (whole body), PGA	Low
Trial 138/139 USA	96	Plantarflexor spasticity post stroke (≥6 weeks prior); AS ≥2	P2, R; 2 cycles (24 wks)	Gastrocnemius, posterior tibialis	NR	• 1^0: AS (ankle) • 2^0: PGA	Unclear
Trial 501 Trial 502 Multi-Country	131	Plantarflexor spasticity post stroke (≥6 weeks prior); AS ≥2	P2, R; 1 cycle (12 wks) Some patients were retreated (same dose) in Trial 502 (N=91); 1 cycle (12 wks)	Gastrocnemius, anterior/posterior tibialis	Physical therapy at baseline: up to 93% of patients Physical therapy by the end of the trial: up to 84% of patients	• 1^0: AS (ankle) • 2^0: PGA	Low
BEST[a] (Borg 2011, Ward 2014, Wissel 2016) Multi-country	273	Upper and/or LLFS post stroke (≥3 mths prior)	P4, R; 1 (or 2) cycle (22-34 weeks), DB; 1 cycle (up to Wk 52), OL	• Ankle • Thigh • Hip	Varied	• 1^0: GAS • 2^0: EQ5D, SF-12v2	Low
Tao 2015 China	23	Plantarflexor spasticity post stroke (≤6 wks prior); MAS ≥1	P2, R; 1 cycle (8 wks)	Gastrocnemius, soleus, posterior tibialis; ES-guided	100%	• 1^0: MAS (ankle)	Low

Abbreviations: AS= Ashworth score; AUC=area under the curve; CGI=clinical global impression of change; DB=double blind; EQ5D= European quality of Life - 5 Dimensions; ES=electrical stimulation; GAS=goal attainment scale; MAS=modified Ashworth score; NR=not reported, OL=open label; PBO=placebo; PGA=Physicians Global Assessment; P2=phase 2, P3=Phase 3; P4=phase 4, R=randomised; sEMG=surface electromyography; SF-12=Short Form 12; Wk=week.

[a] The exact BOTOX® dose and number of injection sites were tailored for the individual patient based on the size, number, and location of muscles involved; the severity of spasticity; and the presence of local muscle weakness (CSR BEST. P33). Primary endpoint at 10-weeks post second injection or week 24 if no second injection (CSR BEST, p91)

[b] Rehabilitation was permitted during the study period, provided that the frequency and program of rehabilitation remained unchanged during the double-blind phase. During the open-label phase, rehabilitation might be changed to one that was considered most appropriate for a subject according to the degree of improvement in his/her spasticity. In this case, the global impression of therapeutic benefit of BOTOX® to rehabilitation was to be assessed at the end of the study. Rehabilitation was prohibited on the day of injection.

Source: compiled during the evaluation from the trial publications and Clinical Study Reports.

6.12 A number of concerns were noted with the evidence, including:

- Some of the included secondary trials were underpowered to detect meaningful differences. Tao 2015 included a very small number of patients (N=25) and Trial 030 was a trial of pulmonary function and was not powered to detect treatment differences in spasticity outcomes.
- Apart from Trial 030 and BEST, all of the included primary and secondary evidence focused on ankle spasticity; in particular, spasticity arising from the plantar/dorsiflexor muscles. The resubmission did not discuss whether results of BOTOX® on ankle spasticity would be transferrable to other muscle groups in the lower limb, particularly as other muscles of lower limb perform different functions and given their differing sizes would also require different dosages. In REFLEX, doses injected in the rectus femoris muscle did not lead to any significant change in MAS. The PSCR stated that the key studies assessed ankle spasticity as the primary endpoint to increase the homogeneity of the population. In the REFLEX trial, patients were able to receive doses of ≤ 100U in optional other muscles, including the flexor digitorum longus and brevis, flexor hallucis longus, extensor hallucis and rectus femoris. The PSCR stated that MAS and CGI was improved in patients who received optional toe flexor injections relative to the ITT population. In addition, there was an increase in the proportion of patients experiencing an improvement of at least 1 MAS in the first 4-6 weeks of the open-label extension phase of REFLEX, during which investigators were permitted to use the maximum dose across all permitted muscles at their discretion. The PSCR contended this was evidence that outcomes were better when investigators were permitted to target affected muscles, and that this supported the transferability of the efficacy of BOTOX® to other muscle groups in the lower limb.
- The proposed PBS criteria stated that BOTOX® is only to be used after standard management has failed or used as an adjunct to physical therapy. In the included trials, the proportion of patients undergoing concomitant physical therapy varied widely; from [redacted]% and [redacted]% in the BOTOX® and placebo arm in REFLEX to 100% in Tao 2015. The proportion of patients who had failed standard management prior to trial entry was uncertain across the trials.
- The secondary trials were generally highly heterogeneous, including patients with varying severity, dosing regimens, concomitant physical therapy, outcome measures, time points and study duration.

Comparative effectiveness

6.13 The main outcome reported in the trials was change in MAS score, which measures the level of resistance to passive movement, and evaluates a combination of soft tissue contracture and spastic dystonia, in addition to spasticity itself. Scale criteria are outlined in Table 5.

Table 5: Description of the Modified Ashworth Scale (MAS)

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

Source: Table 2.4-16, p88 of the submission, and compiled during evaluation

6.14 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.

6.15 The resubmission nominated a reduction of at least one point (MAS ≥ 1) to be the minimally clinically meaningful difference (MCID). Patients attaining this reduction from baseline in MAS were considered responders in the clinical and modelled economic evaluations. 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 (November 2007, Dysport® PSD), and where MAS was supported by improvements in Goal Attainment Scale (GAS) and Global Assessment of Benefit (GAB) scores. 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).

6.16 A change in MAS ≥ 1 from baseline was inconsistent with the continuation criteria in the current PBS listing for focal spasticity of the upper limb.

6.17 Results from the primary and secondary trials are summarised below for: mean change in MAS from baseline, MAS responder, CGI, GAS and health related quality of life (HRQoL). Results of subgroup analyses in REFLEX and meta-analyses for MAS/AS ≥ 3 population in the trials are also presented.

Mean change in MAS from baseline

6.18 Table 6 summarises the results for mean change in MAS score from baseline in the primary trials. The main time points for assessment of MAS outcomes in REFLEX were at Week 4 and 6 and in Trial 512, area under the MAS curve (AUC) was measured from baseline to Week 12. For comparability results for change to each time point are presented.

Table 6: Mean change in MAS score from baseline in the primary trials

Endpoint Weeks	BOTOX® 300-400 U				Placebo				Difference (95%CI), p value
	Baseline		Change		Baseline		Change		
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	
REFLEX									
2	233	4.1 (0.27)	228	-0.7 (0.85)	235	4.1 (0.25)	233	-0.5 (0.79)	**-0.21 (-0.35, -0.06) p=0.006**
4	233	4.1 (0.27)	225	-0.8 (0.93)	235	4.1 (0.25)	229	-0.6 (0.86)	**-0.22 (-0.39, -0.06) p=0.007**
4-6*	233	4.1 (0.27)	233	-0.81 (0.87)	235	4.1 (0.25)	235	-0.61 (0.84)	**-0.20 (-0.36, -0.05); p=0.01**
6	233	4.1 (0.27)	225	-0.8 (0.97)	235	4.1 (0.25)	224	-0.6 (0.92)	**-0.19 (-0.37, -0.02) p=0.027**
8	233	4.1 (0.27)	227	-0.7 (0.89)	235	4.1 (0.25)	228	-0.6 (0.87)	-0.10 (-0.27, 0.06) p=0.220
Trial 512									
1	58	3.3 (0.45)	57	-0.61 (0.68)	62	3.2 (0.43)	62	-0.5 (0.77)	-0.09 (NR) p=0.222
4	58	3.3 (0.45)	56	-0.88 (0.69)	62	3.2 (0.43)	62	-0.43 (0.72)	**-0.46 (NR) p<0.001**
6*	58	3.3 (0.45)	57	-0.91 (0.73)	62	3.2 (0.43)	61	-0.47 (0.71)	**-0.45 (NR) p<0.001**
8	58	3.3 (0.45)	54	-0.82 (0.66)	62	3.2 (0.43)	61	-0.43 (0.68)	**-0.40 (NR) p<0.001**
12	58	3.3 (0.45)	54	-0.56 (0.69)	62	3.2 (0.43)	61	-0.40 (0.58)	-0.15 (NR) p=0.240

Abbreviations: CI = confidence interval; SD = standard deviation.

Analyses: as presented in the References. Note that the means in REFLEX are least-squares means.

* denotes this was a trial primary outcome, P-values and 95% CIs for between-group comparisons were obtained from an ANCOVA model (ITT Population) including treatment and centre as factors, with baseline ankle MAS-B and muscle group injected as covariates.

Source: Table 2.5-1, p108 and Table 2.5.2, p109 of the submission.

6.19 Peak change in ankle MAS from baseline was achieved at Weeks 4 and 6 in the REFLEX trial and at Week 6 in Trial 512, with significant between-group differences at these time points favouring BOTOX®. However, despite the above results reaching statistical significance, the average difference between BOTOX® and placebo was small in magnitude and the average incremental improvement did not exceed the predefined MCID of at least one point reduction in MAS. The effect of BOTOX® waned at eight weeks in REFLEX and at 12 weeks in Trial 512.

6.20 The PSCR stated that the application of the MCID to the mean change in MAS should not result in the interpretation that the treatment effect of BOTOX® was not clinically meaningful. Instead, the difference between BOTOX® and placebo in the proportion of patients who achieved a clinically meaningful improvement in MAS (as defined by an improvement in MAS of ≥ 1 point) reflected the appropriate application of the MCID. This is addressed in the MAS responder analysis below.

6.21 During the open label (OL) phase of REFLEX, all patients received BOTOX® for up to three treatment cycles. Reductions in MAS were maintained over the three treatment cycles for each respective time point, with mean reductions from baseline ranging between -1.2 and -1.4, i.e. they were clinically significant. Similar trends were reported for the OL phase of Trial 512, with mean reductions from baseline ranging from −1.04 to −1.55. In REFLEX, change in MAS waned towards the end of each treatment period, but responses were observed in those who chose to continue with subsequent treatments of BOTOX®. In Trial 512, the change from baseline appeared to be maintained over time (with MAS change > 1 at all time points). However, as the number of patients treated declined considerably in successive cycles (from 97 at Cycle 1 to 27 at Cycle 3 of the OL phase), response rates during the OL studies should

be interpreted in the context of the high rate of discontinuation, which may have occurred due to non-response.

6.22 Most of the secondary trials did not find any significant differences between BOTOX® and placebo treatment for improvement in spasticity from baseline to the timing of assessment. Some exceptions were:

- Trial 030 reported a significant improvement in Ashworth Scale (AS) at Week 6 (BOTOX® 240U versus placebo, difference: -0.6, p=0.009); however, the higher dose of BOTOX® (360U) did not have a significant impact over placebo (difference: -0.4, p=0.361). This trial allowed treatment of upper limb and lower limb muscles at the discretion of the investigator and was powered to assess pulmonary function rather than efficacy. The authors stated that resulting heterogeneity limited the statistical power to detect differences between treatments for lower limb spasticity.
- Tao 2015 reported a significant difference in MAS scores at Week 8 following BOTOX® treatment compared with placebo (p<0.05, actual change from baseline was not reported). The trial was small (N=23).
- Trial 702 found no significant difference between BOTOX® and placebo treatment in its ITT population (patients with AS ≥ 2), results reached statistical significance in the subgroup of patients with AS ≥ 3 (AS scale difference was -0.25 and -0.68 for low and high dose BOTOX®, respectively, versus placebo, p=0.01).

MAS responder analysis

6.23 MAS responders across various time points in the primary trials are summarised in Table 7. The definition of response was a decrease in MAS of at least 1 point from baseline.

Table 7: MAS/AS responders across various time points (MAS reduction ≥1) in the primary trials, during DB phase

Week	BOTOX® 300-400 U			Placebo			BOTOX® vs. Placebo
	n	N	%	n	N	%	*RD (95%CI),* p value
REFLEX (MAS)							
2	103	228	45.2%	75	233	32.2%	**0.13 (0.04, 0.22); p=0.004**
4	117	225	52.0%	89	229	38.9%	**0.13 (0.04, 0.22); p=0.005**
6	120	225	53.3%	88	224	39.3%	**0.14 (0.05, 0.23); p=0.003**
8	111	227	48.9%	90	228	39.5%	**0.09 (0.00, 0.019); p=0.04**
12	73	226	32.3%	52	226	23.0%	**0.09 (0.01, 0.17); p=0.027**
Trial 512 (MAS)							
1	30	58	51.7%	24	62	38.7%	0.13 (-0.05. 0.31); p=0.378
4	38	58	65.5%	19	62	30.6%	**0.35 (0.18, 0.52); p=0.022**
6	39	58	67.2%	22	62	35.5%	**0.32 (0.15, 0.49); p=0.047**
8	36	58	62.1%	20	62	32.3%	**0.30 (0.13, 0.47); p=0.048**
12	24	58	41.4%	21	62	33.9%	0.08 (-0.10, 0.25); p=0.567
Trial 702 (AS)							
12 (AS≥2)	*16*	*54*	*29.6%*	*5*	*29*	*17.2%*	0.12 (-0.06, 0.31); p=0.22
8 (AS≥3)	16	10	62.5%	1	16	6.3%	**0.56 (0.30, 0.83); p=0.001**
12 (AS≥3)	*14*	*31*	*45.2%*	*1*	*17*	*5.9%*	**0.39 (0.18, 0.60); p=0.01**

Abbreviations: AS =Ashworth score, DB=double blind, MAS = modified Ashworth score, RD= risk difference

Note: All data as reported (N values were not adjusted to all randomised patients but was in the meta-analysis). For REFLEX, the same p-values were obtained using a Pearson's chi-square or Fisher's exact test (if ≥ 25% of the expected cell counts were < 5) and a logistic regression model with treatment, baseline ankle MAS-B, and muscle group injected in the model. For Trial 512, Pearson's chi-square tests were conducted for this submission.
Source: Table 2.5.1, p115 of the submission, Dunne 2012 p792 for Trial 702, Table 2.6-15, p145 of the submission.

6.24 Statistically significant differences in proportion of MAS responders between BOTOX® and placebo were observed at Weeks 2, 4, 6, 8 and 12 in REFLEX and Weeks 4, 6 and 8 in Trial 512. The difference between BOTOX® and placebo in responders was much smaller in REFLEX (maximum difference of 14%) compared to Trial 512 (maximum difference of 35%). In both trials the difference between BOTOX® and placebo reduced over time, and by Week 12 the differences between BOTOX® and placebo in the proportion of responders was approximately 9% in both trials.

6.25 Results from Trial 702 suggested that there was no difference in the proportion of responders, defined by the AS for ankle plantar flexor spasticity, between the treatment groups at Week 4, 8, 12 or 16 post-injection. However, among the subgroup of patients with a baseline MAS ≥ 3, there were significant differences between treatment BOTOX® and Placebo groups at Week 8 and Week 12.

Clinical Global Impression (CGI) – physician

6.26 Results of CGI (by physician) change from baseline across the primary trials are summarised in Table 8. The CGI by physician scale used in the REFLEX trial was a 9-point scale indicating functional change from the patient's baseline status from –4 (very marked worsening) to +4 (very marked improvement), whereas in the Trial 512 the CGI was an 11-point scale ranging from -5 (worst possible) to 5 (best possible). As the CGI score rates response to treatment, there are no baseline scores reported.

Table 8: Results of CGI (by physician) across the primary trials: continuous data

Trial ID	BOTOX® Mean (SD)			Placebo Mean (SD)			Mean difference^ (95% CI), p value
	N	Time point	Mean change	N	Time point	Mean change	
REFLEX[a]	**228**	W2	**0.8 (0.9)**	**233**	**W2**	**0.5 (0.85)**	**0.30 (0.14, 0.46) p=0.003**
	233	W 4-6 average	0.86 (0.95)	235	W 4-6 average	0.65 (0.90)	**0.22 (0.05, 0.38) p=0.012**
	227	W8	0.9 (1.04)	228	W8	0.8 (0.99)	0.12 (-0.07, 0.31) p=0.12
	226	W12	0.6 (1.03)	226	W12	0.6 (0.96)	0.00 (-0.18, 0.18) p=0.594
Trial 512	56	W4	1.09 (1.25)	61	W4	0.64 (1.07)	**0.45 (NR), p=0.048**
	56	W6	1.21 (1.56)	61	W6	0.66 (1.18)	**0.56 (NR), p=0.042**
	54	W8	1.13 (1.32)	61	W8	0.59 (1.23)	**0.54[b] (NR), p=0.016**

Note: scores indicate change from the patient's baseline status, from −4 (very marked worsening) to 4 (very marked improvement).
Abbreviations: CI = confidence interval; NR= not reported; SD = standard deviation

[a] Missing values at either week 4 or week 6 were replaced by the non-missing value. The change rate imputation method was used to impute missing values if both weeks 4 and 6 data were missing.

[b] The submission had reported 0.12, and was corrected with data from the CSR.

^ estimated during the evaluation using Review Manager 5.3

Source: Table 2.5-9, 2.5-10, pp 116 and 117 of the submission, CSR Trial 512 (Table 15, p76)

6.27 In REFLEX, patients in the BOTOX® group experienced a significant improvement on the CGI scale compared with those receiving placebo at Weeks 2 and 4/6, but the difference between treatment groups was no longer significant at Week 8. Statistically significant treatment differences favouring BOTOX® were found in Trial 512 at Week 4, 6, and 8.

Goal Attainment Scale (GAS) - physician and patient

6.28 Results of the Goal Attainment Scale (GAS) in the REFLEX trial were reported by patient and by physician. The GAS was used as a measure of functional improvement. Scores ranged from −3 (worse than start) to +2 (much more than expected, improvements clearly exceeded the defined therapeutic goal), based on a 6-point scale. Physicians and patients selected active and passive goals prior to treatment and assessed response following treatment.

6.29 At Week 8, a significantly greater proportion of BOTOX®-treated patients experienced goal improvement of at least 1 point (score ≥ 1) on the GAS based on physician assessment for active and passive goals and patient assessment for active goals compared with placebo-treated patients. However, there were no significant differences between BOTOX® and placebo treated patients with respect to goal attainment at Week 8.

6.30 At Week 12, the proportions of patients who achieved their passive goals (GAS ≥ 0) was significantly higher in the BOTOX® group than placebo (40.4% versus 30.6%, p = 0.033), as assessed by physician. Over the course of the OL phase, both physician- and patient-assessed GAS for active and passive goals generally improved (≈75-90% for both physician and patient assessed active and passive goals from Week 6 post OL treatment 1 to Week 12 post OL treatment 3[2]).

6.31 The primary efficacy variable in BEST was the attainment of the principal active functional goal as assessed by the physician at 10 weeks post-second injection (or Week 24 if no second injection was given). No significant differences between BOTOX® and placebo were found for this outcome (odds ratio = 1.20, 95% C:I 0.70, 2.06, p=0.511).

HRQoL

6.32 HRQoL results (EQ5D-3L and SF36) from the REFLEX trial demonstrated only minimal changes from baseline to Week 6 across all HRQoL domains and instruments and no significant differences between treatment groups. EQ-5D-3L individual patient data (IPD) at Week 6, stratified by MAS response were applied to derive the health state utilities for the modelled economic evaluation.

[2] See REFLEX CSR, Table 14.2-5.4, p443 and Table 14.2-4.4, p430.

Subgroup analysis REFLEX: different injection sites and varying time since stroke Change in MAS

6.33 In REFLEX, patients received mandatory dosing of BOTOX® or placebo, injected at specified sites, totalling 300U and were able to receive up to an additional 100U at specified sites at the discretion of the clinician.

6.34 A subgroup analysis considered response for patients receiving BOTOX® in the toe flexors, flexor digitorum longus (FDL) and/or flexor hallucis longus (FHL). Subgroup results for MAS change from baseline to Week 4-6 in REFLEX based on injection sites are summarised in Table 9.

Table 9: MAS change from baseline to Week 4-6: REFLEX subgroups based on injection sites

Injection site	BOTOX® N=231		Placebo N=233		Mean difference
	N (%)	Mean change from baseline	N (%)	Mean change from baseline	
ITT population	233 (100)	-0.81	235 (100)	-0.61	**-0.20 p=0.01**
Mandatory ankle only (300U)	104 (44.6)	-073	107 (45.5)	-0.58	-0.15 p=0.255
Mandatory ankle + FHL + FDL (400U)	62 (26.6)	-0.98	57 (24.2)	-0.52	**-0.46 p=0.002**
Mandatory ankle + FHL or FDL +/- other muscles (350U-400U)	87 (37.3)	-1.08	92 (39.1)	-0.67	**-0.41 p=0.001**
Mandatory ankle + FHL +/- other muscles (350U-400U)	74 (31.8)	-0.95	67 (28.5)	-0.42	**-0.53 p<0.001**
Mandatory ankle + FDL +/- other muscles (350U-400U)	81 (34.8)	-1.19	83 (35.3)	-0.80	**-0.39 p=0.003**

Abbreviations: FDL= flexor digitorum longus, FHL= flexor hallucis longus, ITT=intention to treat
Bold typography indicate statistically significant results.
Source: Table 2.6.2 (p131), Figure 2.6 2 (p132) of the resubmission.

6.35 The results of the subgroup analysis indicated that BOTOX® injections to the mandatory ankle muscles alone did not lead to any significant differences between BOTOX® and placebo treatment groups in terms of mean change in MAS at Week 4-6 from baseline. However, significant differences between BOTOX® and placebo arms were observed when either FHL and or FDL were also injected.

6.36 The PBAC considered that the treatment effect of BOTOX® could potentially be extrapolated to lower limb focal spasticity more broadly regardless of aetiology. However, the PBAC stated that this was based on biological plausibility rather than definitive trial evidence. The PBAC noted that there was support for BOTOX® use in the treatment of focal spasticity due to aetiologies other than stroke and noted the comments regarding equitable access for non-stroke patients.

Meta-analyses MAS/AS ≥3 population

6.37 Results of a meta-analysis of patients in REFLEX, Study 702 and Study 512 with a baseline MAS/AS ≥ 3 at Weeks 4, 6 and 8 demonstrated that patients treated with BOTOX® injections had a statistically significantly greater improvement in MAS/AS relative to patients who received placebo injections.

6.38 The random effects meta-analysis of the difference in the proportion of responders (defined as ≥ 1 point reduction in MAS/AS score from baseline) between BOTOX® and

placebo was statistically significant and ranged from a pooled risk difference of 21% at Week 6 to 29% at Week 8. However, there was marked heterogeneity across the trials in terms of treatment effects and the robustness of the results may be questionable.

Table 10: Results of responder analysis in PBS population: one-point improvement in MAS at Weeks 4, 6 and 8

Week	BOTOX® 300-400 U		Placebo		Risk Difference (RD)		
	n/N	%	n/N	%	RD (95% CI)	P value	Heterogeneity
Week 4	164/307	53.4%	112/313	35.8%	0.24 (0.06, 0.41)	0.007	Tau^2=0.02; Chi^2=6.09, df=2 (P=0.05); I^2=67%
Week 6	159/291	54.6%	110/297	37.0%	0.21 (0.04, 0.38)	0.01	Tau^2=0.01; Chi^2=3.28, df=1 (P=0.07); I^2=70%
Week 8	157/307	51.1%	111/313	35.5%	0.29 (0.04, 0.54)	0.02	Tau^2=0.04; Chi^2=13.55, df=2 (P=0.001); I^2=85%

Abbreviation: CI = confidence interval; MAS= Modified Ashworth scale; RD= Risk Difference.
Source: This condensed version of the meta-analysis was presented as Table 2, p7, PSCR

Comparative harms

6.39 Overall, more patients treated with BOTOX® experienced AEs including serious AEs compared to patients in the placebo arms of Trial 512 and REFLEX, but the differences did not reach statistical significance. Discontinuations due to AEs were higher in the BOTOX® arms, but the rates were low in both trials. There were no deaths. The most common AEs reported were pain in extremity, nasopharyngitis and falls, but rates were similar in the BOTOX® and placebo groups. In the trials, injection site pain for placebo arms would be associated with sham injections used to maintain blinding. In clinical practice, patients not undergoing BOTOX® treatment would not experience discomfort. It was noted that 2.2% and 5% of patients had reported injection site pain with BOTOX® treatment in REFLEX and Trial 512.

6.40 The AE rates varied significantly across the secondary trials (with 10.1% to 27.6% of patients with treatment related AEs) and were higher than rates reported in the primary trials (5.6% and 12.1% for REFLEX and Trial 512, respectively). In the double-blind phase of BEST, the rate of treatment-related AEs was also significantly higher in the BOTOX® group 14 (10.1%) versus placebo 5 (3.7%) (Pearson's Chi square test p=0.05).

Benefits/harms

6.41 A summary of the comparative benefits and harms for BOTOX® versus placebo is presented in Table 11. The main endpoints described in the trials have been used.

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

	BOTOX® n/N	PBO n/N	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				BOTOX®	PBO	
Benefits						
Continuous outcome: MAS change from baseline to Week 4-6						
	BOTOX®			PBO		Mean difference (95% CI)
	N	Mean Δ baseline	SD	N	Mean Δ baseline	SD
Average of Week 4-6						
REFLEX:	233	−0.81	0.87	235	−0.61	0.84	**-0.20 (-0.36, -0.05)**
Week 6						
Trial 512	57	−0.91	0.73	61	−0.47	0.71	**-0.45 (-0.70, -0.18)**
	BOTOX® n/N	**PBO n/N**	**RR (95% CI)**	**Event rate/100 patients***		**RD (95% CI)**
				BOTOX®	**PBO**	
Dichotomous outcome: MAS responder (Δ≥1) Week 6						
REFLEX	120/225	88/224	1.36 (1.11, 1.66)	53.3	39.3	**0.14 (0.05, 0.23)**
Trial 512	39/58	22/62	1.89 (1.30, 2.77)	67.2	35.5	**0.32 (0.15, 0.49)**
Dichotomous outcome: GAS REFLEX Week 8						
Physician Active Slight improvement	153/225	128/228	1.21 (1.05, 1.40)	68.0	56.1	**0.12 (0.03, 0.21)**
Physician Passive Slight improvement	139/213	121/217	1.17 (1.00. 1.36)	65.3	55.8	**0.09 (0.00, 0.19)**
Patient Active Slight improvement	141/212	118/215	1.21 (1.04, 1.41)	66.5	54.9	**0.12 (0.02, 0.21)**
Continuous outcome: CGI Physician to Week 4-6						
	BOTOX®			PBO		Mean difference (95% CI)
	N	Mean	SD	N	Mean	SD
Average of Week 4-6						
REFLEX	233	0.86	0.95	235	0.65	0.90	**0.22 (0.048, 0.383)**
Week 6						
Trial 512	56	1.21	1.56	61	0.66	1.18	**0.56 (0.05,1.05)**

Abbreviations: MAS=modified Ashworth scale; GAS=goal attainment scale, CGI=clinical global impression; RD = risk difference; RR = risk ratio; TEAE=treatment emergent adverse event, NR=not reported.
Source: compiled during the evaluation based on efficacy results reported in the submission.

6.42 On the basis of direct evidence presented by the resubmission the comparison of BOTOX® and placebo after one dose in:

A) REFLEX resulted in:

- An additional 0.2 point reduction in MAS score from baseline to Week 4-6. Although this was a statistically significant reduction, the selected MCID (MAS ≥ 1 reduction) was not met, and therefore the clinical significance of this result was uncertain.
- For every 100 patients treated with BOTOX® in comparison to placebo, approximately 14 additional patients would have a MAS response (reduction ≥ 1) at 6 weeks.
- A mean difference of 0.22 points on the CGI score at Week 4-6, indicating functional improvement.

- For every 100 patients treated with BOTOX® in comparison to placebo, approximately 12 additional patients reported a "slight improvement" towards achieving their goals on the GAS at 8 weeks.

B) Trial 512 resulted in:

- An additional 0.45 point reduction in MAS score from baseline to Week 6. Even though, there was a significant difference with placebo, the selected MCID (MAS ≥ 1 reduction) was not met, and therefore the clinical significance of this result is uncertain.
- For every 100 patients treated with BOTOX® in comparison to placebo, approximately 32 additional patients would have MAS response (reduction ≥ 1) at 6 weeks.
- A mean difference of 0.56 points on the CGI score at Week 6, indicating functional improvement.

Clinical claim

6.43 The resubmission described BOTOX® added to standard management as superior in terms of effectiveness and non-inferior in terms of safety compared to placebo (or standard management alone).

6.44 The resubmission made a number of specific claims, including:

- The results of the MAS analyses indicate that BOTOX® treatment, added to standard management, reduces the severity of spasticity to a significantly greater extent than placebo. The ESC noted that although the trials demonstrated significant differences between BOTOX® and placebo in mean change from baseline in MAS, the differences were small and did not exceed the predefined MCID.
- A significantly greater number of patients achieved a response measured as at least one point reduction in MAS from baseline following BOTOX® treatment versus placebo (see Table 6). In the REFLEX trial, the maximum difference in the proportion of responders between BOTOX® and placebo was 14%, 95% CI: 0.05, 0.23, at 6 weeks. The ESC considered this magnitude of difference to be small.
- There were no significant differences between BOTOX® and placebo groups in adverse events and no safety signals identified in the extended safety review. While this was an accurate description of the data, it was noted that total AEs were numerically higher in those treated with BOTOX® than placebo. In addition, to maintain blinding, the trials had compared BOTOX® injections with sham injections to the targeted muscles, which will not occur in clinical practice. It was noted that 2.2% and 5% of patients had reported injection site pain with BOTOX® treatment in REFLEX and Trial 512.

6.45 Overall, the ESC considered the resubmission's claim of superior efficacy over placebo was uncertain. Although BOTOX® resulted in a statistically significantly greater reduction in MAS score from baseline, clinically meaningful improvements in MAS

occurred in only 14% more patients in the BOTOX® arm compared with the placebo arm in the main study (REFLEX).

6.46 The ESC considered the resubmission's claim of non-inferior safety compared to placebo was not reasonable given that at the very least, BOTOX® injections would be associated with additional injection site pain compared to patients who do not receive injections.

Economic analysis

6.47 The resubmission presented a stepped economic evaluation based on direct randomised trials:

- Step 1: A 12-week cost-effectiveness (cost per responder) analysis based on results from the randomised placebo-controlled phase of the REFLEX trial.
- Step 2: A 24-week cost-effectiveness (cost per responder) analysis based on the proposed PBS restriction and results from the randomised and extension phases of the REFLEX trial.
- Step 3: A 5-year modelled cost-utility analysis, based on extrapolated and transformed results of the REFLEX trial, in conjunction with other inputs from appropriate local and global sources.

Table 12: Key components of the economic evaluation

Component	Steps 1 and 2	Step 3	Justification/comments
Type of analysis	Cost-effectiveness analysis (CEA)	Cost-utility analysis (CUA)	This was appropriate
Outcomes	Responder analysis (improvement of ≥ 1 MAS point)	Quality adjusted life years (QALYs) gained	Although this was consistent with the clinical data and the updated proposed PBS restriction requested in the PSCR, it conflicted with the current upper limb restriction, which defined response as a reduction in MAS of > 1. A sensitivity analysis was not presented in the submission for response defined as MAS > 1.
Time horizon	12 weeks AND 24 weeks	5 years in the model versus 12 weeks in the double blind phase (REFLEX) and an additional 48 weeks in the open label extension.	This was appropriate
Method(s) used	Decision analysis	Markov cohort model, cohort expected value analysis.	This was appropriate
Health states/ Utilities	Not applicable	– Entry (0.504) – Response (0.553) – Non-response (0.525) – Last line treatment (0.504) – Dead	The ESC considered application of a utility based on response across an entire cycle when response does not occur at the beginning of the cycle and begins to wane by the end of the cycle overestimates the utility gain, and recommended a half cycle correction. The ESC considered that the last line health state might be better represented by the utility value applied in the non-response health state, as treatment is still given.
Cycle length	Not applicable	12 weeks	This was appropriate. The ESC noted that there was no half cycle correction.
Transition probabilities	Not applicable	- Probability of response at entry was based on MAS response in the DB phase of REFLEX. - IPD data from REFLEX were used to derive: i) the probabilities of continued response in the BOTOX® group and ii) health state utilities according to response (using EQ5D-3L data collected in the trial and transformed using Australian weights Viney 2011). - Post-stroke adjusted Australian mortality rates were from ABS data.	There is a high level of uncertainty regarding the probability of continued response in both branches of the model due to the lack of long-term data. The probabilities of continued response were derived from REFLEX data, but the trial only included 4 treatment cycles for BOTOX® and one treatment cycle for placebo (DB phase only). Therefore, there was no data on continued response in the placebo group, and approximately 1-year data for BOTOX® treatment. Furthermore, in the study, only responders tended to continue therapy, so the results are likely to favour BOTOX®. The ESC noted that the model does not adequately account for the natural history of stroke by incorporating the likelihood of non-fatal recurrent stroke.
Costs	Drug and administration and physiotherapy cost	Drug and administration costs, physiotherapy cost, cost for transition to last line therapy ($[redacted]), last line management cost (physiotherapy).	Unit costs used were reasonable. The ESC noted that the adjunctive physiotherapy cost per cycles of $105.08 was for one session only. Patients would likely receive multiple sessions.
Software	Microsoft Excel 2016	TreeAge Pro 2018	This was appropriate

Abbreviations: DB=double-blind, IPD=individual patient data, EQ5D-3L=EuroQol 5 domain 3 level multi-attribute utility instrument. ABS=Australian Bureau of Statistics. Source: Table 3.1-1, p157 of the resubmission.

6.48 Patients with moderate to severe spasticity of the lower limb (MAS ≥ 3) began the model in the entry state and received their first treatment (Cycle 0). Patients who responded (MAS ≥ 1) transitioned to the Response state, while those who did not transitioned to the Non-response state. Patients in the Response state continued to receive treatment for as long as clinical benefit was maintained; moving to the Non-response state upon treatment failure. In Cycle 1 only, patients in the Non-response state were assumed to receive another cycle of treatment and may register a "late" response and transition to the Response state. In all subsequent cycles, patients transitioned through the Non-response state for a single cycle before transitioning to Last line. Background all-cause mortality, adjusted for the post-stroke population was applied equally to all treatment groups and health states from Cycle 1.

6.49 The probabilities of response at entry were obtained from a post hoc analysis of individual patient data from the randomised phase of REFLEX. The ESC noted these were based on a patient achieving a response at any time during the 12 week cycle. The probabilities of response in individuals who had previously responded to BOTOX® treatment were based on further post hoc analyses of independent patient data from the open label phase of REFLEX, which incorporates up to four cycles of treatment. In the absence of long term follow up data, the continuation rate applied in Cycle 4 was assumed to remain constant for the duration of the time horizon. The ESC considered that the proportion of patients achieving a response in the model was considerably higher than demonstrated in the clinical trials – see Figure 1.

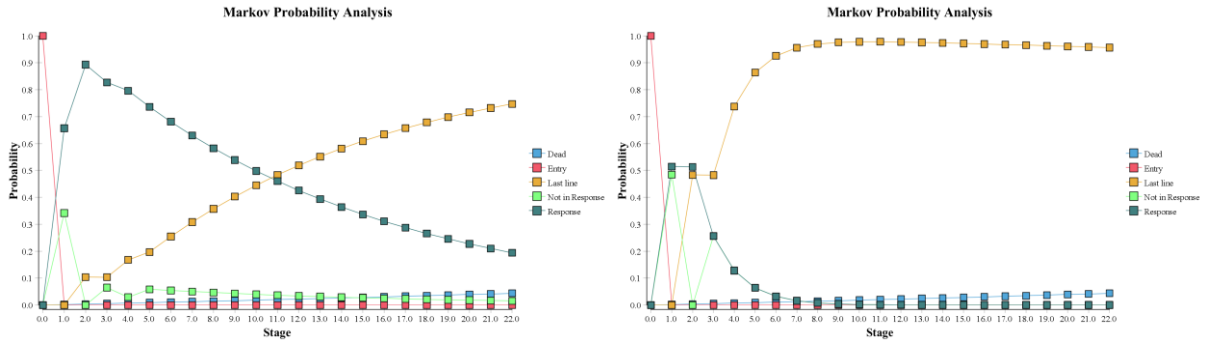
6.50 In the absence of published evidence of the effectiveness of subsequent periods of standard of care, the model assumed that 50% of patients would continue to maintain clinical benefit to each subsequent treatment cycle, with 50% progressing to Last line.

6.51 AEs and injection site reactions were not considered in the model. The resubmission's justification for this was "the use of BOTOX® for treatment of focal spasticity is well established, with an acceptable safety profile and adverse event rates similar to placebo in randomised trials". The PSCR stated that the low rate of injection site reactions and the small impact on quality of life justified their omission from the CUA. The ESC considered that the impact of such short-term disutilities (injection site reactions) would be unlikely to materially influence the model.

6.52 Figure 1 illustrates Markov traces from the TreeAge model.

Figure 1: Comparative Markov traces over 5 years (60 months) for BOTOX® + SOC and SOC

BOTOX® + SOC **SOC**



Source: TreeAge model file

6.53 The population considered in the economic evaluation was based on the REFLEX trial. The ESC noted that there were a number of important discrepancies between patients and the circumstance of use in the trial and the model:

- Patients in REFLEX had ankle spasticity, and the effectiveness of BOTOX® in this location may not be transferable to other joints in the lower limb. The PSCR argued that the effectiveness of BOTOX® may be transferable across lower limb muscle groups (see paragraph 6.12).
- The use of concomitant physical therapy in REFLEX (approximately [redacted]% of the model population) might underestimate physical therapy/rehabilitation use in Australia as the RMSANZ recommends physical therapy for all patients treated with BOTOX® in Australia.
- The model applied a constant probability of response of 0.9276 over the 5 year time horizon. This also implied continuous use of BOTOX® at a rate of ≈ 93% of responders, which was much higher than the BOTOX® utilisation rate reported in the DUSC report in which 68% of patients received less than four treatment cycles of botulinum toxin. In REFLEX, 18% of patients who entered the open label phase had discontinued by the end of the last treatment cycle. This proportion was even higher in Trial 512, where 72% of patients who started the open label phase had dropped out by the last evaluation. Patients in the BOTOX® branch of the model have no option for discontinuation or decline in utilisation of BOTOX® over time. The PSCR stated that the continued response rate was estimated from the OL extension phase of the REFLEX trial, in which patients received up to four cycles of treatment, and that this continuation rate was only applied to patients who met the proposed PBS continuing criteria (decrease in MAS of at least 1). Additionally, the PSCR stated that there was no reason to believe that the treatment effect would diminish over time. The ESC considered that this approach resulted in a considerably higher proportion of patients achieving a response in the model compared with the trials.

- The model assumed that all patients who do not respond to treatment transition to last line. A proportion of patients in the last-line health state were expected to undergo tendon transfer surgery (5%) or receive an intrathecal baclofen pump (5%).

6.54 Table 13 provides a summary of the key drivers in the modelled economic evaluation.

Table 13: Key drivers of the model

Description	Method/Value	Impact
Extrapolation	The probabilities of response in individuals who had previously responded to BOTOX® treatment were based on further post hoc analyses of IPD from the open label phase of REFLEX, which incorporates up to 4 cycles of treatment. In the absence of long term follow up data, the continuation rate from cycle 4 to 5 was assumed to remain constant for the duration of the time horizon. Continued response was assumed to be 93% of responders remaining in the response health state each cycle in the model over 5 years. When lower hypothetical continued response rates were used, the ICER increased considerably (in one scenario a 10 fold increase from base case).	Very High, favours BOTOX®.
Costs	The proportion of patients using physiotherapy in REFLEX was low (around 30%). In the base case the same physiotherapy rate (average) for the BOTOX® and SOC groups were used in both BOTOX® and SOC groups. Applying actual per treatment arm rates of physiotherapy had increased the ICER, furthermore as the proportion of patients using physiotherapy increased (such as when rates Trials 501/502 which was closer to rates reported based in the ASPIRE registry study), the ICER increased considerably (3 fold increase).	High, favours BOTOX®
Utilities	The ESC considered application of a utility based on response across an entire cycle when response does not occur immediately and begins to wane by the end of the cycle overestimated the utility gain. The ESC suggested half cycle correction. The ESC considered that use of baseline utility for last line was not consistent with the clinical evidence and didn't account for the likely benefit of alternative treatments in last line (including surgery).	High, favours BOTOX®

Source: compiled during the evaluation.

6.55 Table 14 provides the results of the stepped economic evaluation. The base case values were corrected during the evaluation to: i) correct a misalignment between reported and applied continued response rate in Cycle 1 (applying 93% rather than 100%); and ii) reflect the differential physiotherapy utilisation rates in the REFLEX trial. These values were applied to Step 3 (CUA) and should have been used in Steps 1 and 2. Instead, the resubmission had applied the average of the two (35.3%), which was not appropriate.

6.56 In the PSCR, the sponsor noted that they accepted the minor amendments relating to differential physiotherapy. However, the sponsor clarified that the proposed PBS listing permits two treatments to determine response, and maintained that 100% of patients would receive two injections in the base case of the model. Those in the non-response state after Cycle 0 can enter the response state after Cycle 1 only. Updated results are presented below.

Table 14: Results of the stepped economic evaluation

Data	Costs			Health outcomes			Incremental cost-effectiveness ratio
	BOTOX® + SOC	SOC	Increment	BOTOX® + SOC	SOC	Increment	
Step 1: 12 Week double-blind trial based CEA, MAS response at any time[a]	Drug, administration and physiotherapy costs			Proportion of responders			Cost/responder
	$ [redacted]	$ [redacted]	$ [redacted]	65.80%	51.50%	14.30%	$ [redacted]
Step 2 – 24 Weeks extended double-blind + open label based CEA, MAS response at any time[a]	$ [redacted]	$ [redacted]	$ [redacted]	89.60%	51.50%	38.10%	$ [redacted]
Step 3: CUA, 5-year Markov Cohort Model	Discounted costs			Discounted QALYs			**Cost/QALY**
	$ [redacted]	$ [redacted]	$ [redacted]	2.4019	2.3102	0.0918	**$** [redacted]
	Undiscounted costs			Undiscounted QALYs			Cost/QALY
	$ [redacted]	$ [redacted]	$ [redacted]	2.6308	2.5309	0.0999	$ [redacted]

CEA = cost-effectiveness analysis, CUA= cost-utility analysis, QALY = quality-adjusted life year, SOC = standard of care

[a] Proportion of physiotherapy was amended to [redacted]% and [redacted]% for BOTOX® and SOC, respectively.

Source: Table 3.8.1, p179, and Table 3.8.6, p187 of the resubmission.

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

6.57 Overall, the ICER was potentially higher than that estimated in the base case. The probability of continued response in the BOTOX® group was the key driver of the model, with slight decreases having a great impact on the ICER. A sensitivity analysis in which the continued response rate was decreased to 0.90 in Cycle 2 and 0.80 in Cycle 3 increased the ICER $45,000/QALY - $75,000/QALY; assuming a gradual reduction in response to 0.68, increased the ICER to $105,000/QALY - $200,000/QALY.

6.58 A sensitivity analysis in which the utility value for the last line health state was changed to that for a non-responder (i.e. from 0.504 to 0.525) increased the ICER to$15,000/QALY - $45,000/QALY.

Drug cost/patient/treatment cycle: $[redacted]

6.59 This was calculated in the model based on the DPMQs weighted for proportional private and public use.

Estimated PBS usage & financial implications

6.60 A market share approach using a combination of PBS utilisation and published epidemiological data were adopted to estimate financial impacts of the proposed listing. This was reasonable.

6.61 The resubmission's estimates had included utilisation and costs associated with treatment of lower limb spasticity associated with causes other than stroke, i.e. traumatic brain injury (TBI) and spinal cord injury (SCI). This was not appropriate in the base case as the requested listing was specific to lower limb focal spasticity post-stroke. The financial implications below are relevant to the post-stroke population only.

6.62 Table 15 presents the estimated net financial implications for the proposed listing of BOTOX® for lower limb spasticity following stroke over the first six years of listing. A number of coding errors and inappropriate assumptions were made by the resubmission in its estimates and the results presented below were corrected:

- for an error that led to a double counting of the number of new scripts in patients with lower limb focal spasticity in the resubmission's estimates; and
- using recalculated proportion of patients accessing RPBS script based on PBS item 10999X (BOTOX® in upper limb focal spasticity) of 0.6% instead of 0.3%.

Table 15: Estimated net cost of BOTOX® to the PBS/RPBS (LLFS post-stroke population)

Estimates	Year 1 (2019)	Year 2 (2020)	Year 3 (2021)	Year 4 (2022)	Year 5 (2023)	Year 6 (2024)
Total numbers of vials for BOTOX® for ULFS following stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of vial numbers with introduction of LLFS post stroke[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total script numbers [a, b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient co-payment [a, b]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
PBS cost (net copayments)[a, b]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
RBPS cost (net copayment)[a, b, c]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net PBS/RPBS cost[a, b, c]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net MBS cost[a,b]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to health budget [a, b, c]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Abbreviations: LLFS = lower limb focal spasticity

Italics indicate results generated during the evaluation using the "Financial implications" spreadsheet provided with the resubmission.

[a] calculation using the corrected value [redacted]% annual increase instead of [redacted]%, Excel file 'Financial implications'.

[b] amended during the evaluation to only reflect estimates for the requested population of patients with LLFS post-stroke

[c] RPBS cost estimated from the 0.6% access rate versus PBS.

Source: Re-estimated during the evaluation applying the above corrections and using the provided Financial implications" Excel file.

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

6.63 The total estimated cost to government was $[redacted] million over the first six years of listing for lower limb focal spasticity post-stroke. The resubmission included MBS item 18360 for BOTOX® injection, but had omitted the cost associated with specialist follow-up consultations associated with BOTOX® injections. When this was added during the evaluation (MBS 116, $65.20 at 85% benefit) the cost increased to $[redacted] million over six years.

6.64 The DUSC advised that the following assumptions may underestimate the actual utilisation of BOTOX®:

- The submission requested a grandfathering listing, but did not include an estimate of the number of grandfathered patients. The DUSC considered that there may be a significant number of grandfathered patients.

- The submission assumed that the removal of the four treatment limit in the lower limb would increase utilisation by [redacted]%. The DUSC considered that this increase may be higher in practice as patients are living longer following stroke and rehabilitation practices are changing.
- DUSC considered that prescribers may make treatment continuation decisions on the basis of functional improvements rather than the MAS improvement criterion. This may increase utilisation.

6.65 The DUSC considered that the following factors may result in an overestimation of utilisation:

- The discontinuation rate is likely to be higher in clinical practice than was estimated ([redacted]%). Treatment uptake was assumed to be [redacted]%; however, it is likely to be lower in clinical practice.
- An annual increase of [redacted]% in the number of vials dispensed was assumed to remain constant over the first six years. This was uncertain.

Quality Use of Medicines

6.66 The resubmission stated there would be no changes to the Botulinum Toxin Program arrangements resulting from the current submission. The Botulinum Toxin Program ensures that PBS supplies of BOTOX® are supplied directly to doctors responsible for performing the injections, and removes the ability for individual patients to handle the packs.

6.67 The PSCR reported that localisation techniques, such as electromyography, muscle ultrasound or electrical stimulation, are commonly used in Australia to facilitate needle placement. The ESC acknowledged that sub-optimal targeting of botulinum toxin injections to the affected muscles may occur in clinical practice.

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

7 PBAC Outcome

7.1 The PBAC deferred making a recommendation on the Section 100 Authority Required listing of botulinum toxin type A (BOTOX®) for the treatment of lower limb focal spasticity following stroke. The PBAC requested that the sponsor address issues raised by the Committee regarding the proposed listing, economic model and pricing.

7.2 In deciding to defer, the PBAC noted the clinical need in the proposed population and acknowledged that, for some patients, a clinically meaningful response defined by an improvement in the Modified Ashworth Scale (MAS) of at least one was achieved, and that improvements in MAS were accompanied by other functional improvements.

7.3 The PBAC acknowledged the consumer comments, which were supportive of listing BOTOX® for lower limb spasticity following a stroke. The PBAC also noted that the Stroke Recovery Association, NSW endorsed the use of BOTOX® in this population and

considered the advice received during the sponsor hearing was informative.

7.4 The PBAC noted that the two key trials, REFLEX and Trial 512, consisted of a single injection during a randomised, double blind phase, followed by up to three injections in an open label phase. The PBAC considered that there was a lack of comparative evidence beyond the first injection and insufficient evidence to inform dosing intervals or the benefit of continuing therapy, particularly beyond the first year of treatment. The PBAC also noted the limited data for the treatment of spasticity other than that causing plantar flexion of the ankle or equinovarus foot deformity.

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

7.6 The PBAC noted that the primary outcome of the trials, which was a reduction in MAS score of at least one, and which was the proposed PBS continuation criteria, was not consistent with the continuation criteria for BOTOX® use in the treatment of focal spasticity following stroke in the upper limb, which required a reduction in MAS of greater than one.

7.7 The PBAC considered that there were aspects of the proposed restriction that would benefit from further clinical input, including:

- confirmation of how BOTOX® is used in patients who continue to respond to treatment and the appropriateness of limiting use to four treatments in the first year and two treatment per year from Year 2; and
- the change from baseline in MAS score after two treatments that would most accurately reflect a patient relevant clinical response (currently proposed as a change in MAS of at least one point).

7.8 In considering the comparative evidence following the first injection cycle, the PBAC noted that BOTOX® treatment resulted in:

- a statistically significantly greater reduction in MAS from baseline compared to placebo, although this difference did not exceed the predefined minimal clinically important difference (MCID) of at least a one point reduction in MAS score;
- a small, but statistically significant, proportion of MAS responders in both the REFLEX (maximum risk difference (RD) = 0.14; 95% confidence interval (CI): 0.05, 0.23) and 512 (maximum RD = 0.35; 95% CI: 0.18, 0.52) trials; and
- some statistically significant improvements in Clinical Global Impression scores and Goal Attainment Scores.

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

7.10 The PBAC considered that BOTOX® was inferior in terms of safety compared to standard of care/placebo.

7.11 The PBAC noted that the economic model was a cost-utility analysis based on a stepped evaluation of the MAS results from the REFLEX trial. The PBAC considered that the approach was appropriate and that the model time horizon (five years) was consistent with the clinical view.

7.12 The PBAC noted that the model was based on the proposed continuation criteria, that is, those who had a reduction in MAS of at least one were considered to continue receive treatment beyond two cycles. The PBAC considered the use of the proposed continuation criteria in the model was reasonable and that a change in MAS score of at least one, although inconsistent with the current continuing criteria for upper limb spasticity, was consistent with the trial evidence. However, given the inconsistency with the existing upper limb continuation criteria, the PBAC considered that applying alternative criteria as sensitivity analyses would be informative. The model applied a constant probability of response 0.9276 over the five year time horizon. The PBAC considered that this approach resulted in a considerably higher proportion of patients achieving a continued response in the model compared to in the REFLEX trial (in which 18% of patients discontinued treatment in the open label phase) and the May 2018 DUSC report (in which 68% of patients received less than four cycles of botulinum toxin). In addition, the PBAC noted that the incremental cost-effectiveness ratio was highly sensitive to changes to the probability of response.

7.13 The PBAC considered that a more appropriate base case would:

- incorporate the discontinuations observed in the open label phase of the REFLEX trial (18%) as non-responders;
- apply a frequency of retreatment that was consistent with that suggested by the PBAC, i.e. four treatments in the first year, followed by two treatments in subsequent years;
- apply the non-responder utility value to the last-line health state, as recommended by ESC; and
- result in an ICER of $15,000 - $45,000 per quality adjusted life year.

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

7.15 The PBAC noted the relative lack of clinical evidence in patients with spasticity due to aetiologies other than stroke. The PBAC considered that while there was a biologically plausible rationale for the use of BOTOX® in these patients, there was a high level of uncertainty in effect, cost-effectiveness and expected utilisation.

7.16 The PBAC considered that the uncertainty surrounding the magnitude of the treatment effect of BOTOX® was unlikely to be reduced by future high quality data. The PBAC considered that the uncertainty surrounding the incremental benefit of BOTOX® could be mitigated through the requested price or the implementation of an

utilisation cap.

7.17 In considering the proposed listing, the PBAC:

- agreed that patients should be permitted up to two cycles to achieve the continuation criterion;
- 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 resubmission, 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 BOTOX® use in upper limb spasticity would also be helpful.
- 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.

7.18 The PBAC advised that a minor resubmission would be required to address the recommended changes to the restriction and the economic model and the PBAC's pricing concerns.

7.19 The PBAC recommended that, if recommended for listing, the Early Supply Rule should not apply.

7.20 The PBAC recommended that, if recommended for listing, botulinum toxin type A should not be eligible for prescribing by nurse practitioners.

7.21 The PBAC recommended that botulinum toxin type A should be treated as interchangeable on an individual patient basis with other forms of botulinum toxin (Dysport® and Xeomin®).

Outcome:
Deferred

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

The sponsor had no comment.