PUBLIC SUMMARY DOCUMENT

Product: Botulinum toxin type a purified neurotoxin complex, lyophilised powder for injection, 100 units, Botox®

Sponsor: Allergan Pty Ltd

Date of PBAC Consideration: July 2012

1. Purpose of Application

Extend the current Section 100 (Botulinum Toxin Program) listing to include the treatment of urinary incontinence due to neurogenic detrusor overactivity in patients who are not adequately managed by anti-cholinergic medication.

2. Background

Botulinum toxin type A had not been previously considered by the PBAC for the treatment of urinary incontinence.

3. Registration Status

On 2 March 2012, Botox was registered by the TGA for the requested indication:

- Treatment of urinary incontinence due to neurogenic detrusor overactivity resulting from a defined neurological illness (such as spinal cord injury or multiple sclerosis) and not controlled adequately by anticholinergic agents. This does not include idiopathic overactive bladder.

Botox is also registered by the TGA for the following indications:
Prophylaxis of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine).
Treatment of strabismus in children and adults.
Treatment of blepharospasm associated with dystonia, including benign blepharospasm and VII nerve disorders (specifically hemifacial spasm) in patients twelve years and older.
Treatment of cervical dystonia (spasmodic torticollis).
Treatment of focal spasticity of the upper and lower limbs, including dynamic equinas foot deformity, due to juvenile cerebral palsy in patients two years of age and older.
Treatment of severe primary hyperhidrosis of the axillae.
Treatment of focal spasticity in adults.
Treatment of spasmodic dysphonia.
Temporary improvement in the appearance of upper facial rhytides (glabellar lines, crow's feet and forehead lines) in adults.

4. Listing Requested and PBAC's View

Section 100 Botulinum Toxin Program
Authority Required
Treatment of urinary incontinence due to neurogenic detrusor overactivity, as demonstrated by a urodynamic study, in a patient who is not adequately managed by anti-cholinergic therapy.
Inadequate management by anti-cholinergic therapy is shown by an insufficient response or if the patient experiences intolerable side effects necessitating permanent withdrawal from treatment.
Treatment should be discontinued if the patient does not show response after the first treatment. Treatment response is defined as a 50% or greater reduction from baseline in urinary incontinence infrequency assessed at 6–12 weeks after treatment.

Maximum number of treatments per year is two, with no less than six months to elapse between treatments.

The PBAC noted that the requested restriction did not restrict treatment to MS and SCI patients and therefore use in other patient groups (spina bifida, stroke and Parkinson disease) with UI due to NDO would be likely, although the PBAC considered that the number of patients with spina bifida was likely to be small and that while there may be some utilisation in Parkinson disease, the Committee noted that only some patients with Parkinson disease would be able to self-catheterise. The PBAC also noted that patients needed to have at least fourteen UI episodes per week to enter into trials 515 and 516, but the proposed PBS restriction did not include a definition of UI at baseline. Therefore the proposed PBS population could include patients with a reduced frequency of UI for which the efficacy of botulinum toxin is unknown.

5. Clinical Place for the Proposed Therapy

The detrusor is the primary muscle lining the bladder wall and is responsible for emptying the bladder. In patients with neurogenic detrusor overactivity (NDO), spontaneous detrusor contractions lead to a heightened sense of bladder fullness, increased bladder pressure, reduced storage volume, increased urinary frequency, and incontinence.

Neurogenic detrusor overactivity occurs as a result of an underlying neurologic disorder, occurring frequently in patients with multiple sclerosis and spinal cord injury, as well as in patients with myelomeningocele (a common type of spina bifida) and Parkinson Disease.

Currently, treatment options for NDO include non-pharmacological management including lifestyle modifications (e.g. moderating fluid intake, pre-emptive voiding, avoiding dietary bladder irritants), the use of pads, portable urinals and clean intermittent catheterisation; and pharmacological management including use of oral anti-cholinergic medications. Upon failure of treatments, patients may be directed to more invasive surgical interventions such as augmentation cystoplasty or sacral neuromodulation, which involves the implantation of a neurostimulation device.

The submission proposed that botulinum toxin would be used for patients with NDO who are refractory or intolerant to anti-cholinergic medications, prior to the consideration of invasive surgical procedures.

6. Comparator

The submission nominated best supportive care (BSC) as the comparator, consisting of non-pharmacological management such as lifestyle modification or behavioural therapy (e.g. moderating fluid intake, pre-emptive voiding, avoiding dietary bladder irritants), and the use of pads, portable urinals and clean intermittent catheterisation. This was considered appropriate by the PBAC.

7. Clinical Trials

The submission presented two randomised trials (Study 515 and 516) comparing Botox (200 U and 300 U) to BSC in 691 patients with urinary incontinence due to NDO as a result of multiple sclerosis (MS) or spinal cord injury (SCI). Four supportive trials were also presented; three comparing Botox to best supportive care (two in patients with either MS or SCI and one trial with SCI patients only) and one single arm long-term follow-up study

(Study 094) of trials 515 and 516. Trial 094 was only relevant for the extended assessment of comparative harms.

Studies 515 and 516 had a three week screening period prior to randomisation. Within both trials, patients who had at least 14 urinary incontinence (UI) episodes per week at baseline were initially randomised to BSC (placebo injections), 200 U Botox, or 300 U Botox in a 1:1:1 ratio. Both trials had a 12-week placebo-controlled blinded phase followed by a 52-week open-label phase where all patients received Botox and placebo patients crossed over to active therapy for the subsequent treatment cycle. Results for the 300 U Botox arm were not presented, as the recommended dose in the approved PI is 200 U.

The table below details the published trials and associated reports in the submission.

Trial ID / First author	Protocol title / Publication title	Publication citation
Direct randomised trial(s)		
Study 515	A multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the safety and efficacy of a single treatment with two dose levels of BOTOX® (botulinum toxin type A) purified neurotoxin complex followed by treatment with BOTOX® in patients with urinary incontinence due to neurogenic detrusor overactivity	(191622-515)
Chapple CR et al	Phase 3 efficacy and safety study of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity.	BJU Int 108[Suppl 1], 20. 2011.
Study 516	A multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the safety and efficacy of a single treatment with two dose levels of BOTOX® (botulinum toxin type A) purified neurotoxin complex followed by a treatment with BOTOX® in patients with urinary incontinence due to neurogenic detrusor overactivity.	(191622-516)
Cruz F. et al	Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: A randomised, double-blind, placebo-controlled trial.	Eur Urol 2011;60(4):742-50.
Supportive trials		
Study 511	A multicentre, double-blind, randomised, placebo-controlled, parallel group study to evaluate the safety and efficacy of BOTOX® (botulinum toxin, type A) purified neurotoxin complex in subjects with urinary incontinence caused by detrusor hyperreflexia.	(191622-511)
Hollingworth, W, et al	Exploring the impact of changes in neurogenic urinary incontinence frequency and condition-specific quality of life on preference-based outcomes.	Quality of Life Research (2010)19(3): 323-331.
Schurch B, et al	Botulinum toxin type A is a safe and effective treatment for neurogenic urinary incontinence: Results of a single treatment, randomized, placebo controlled 6-month study.	J Urol 2005;174(1): 196-200.

Schurch B, et al	Botulinum toxin A improves bladder function without drug-related adverse events in patients with neurogenic detrusor overactivity: Results from a randomised, double-blind, placebo-controlled study.	Eur Urol 2007;52(3):850-9.
Schurch B, et al	Botulinum toxin A in neurogenic bladder: Are there any patient predictors of response?	Eur Urol 2006;5(11):679-84.
Schurch B, et al	Reliability and validity of the incontinence quality of life questionnaire in patients with neurogenic urinary incontinence.	Arch Phys Med Rehabil 2007;88(5):646-52.
Schurch B, et al	Subgroup analysis to determine impact of patient demographics on urodynamic response to focal administration of botulinum toxin A.	Neurourol Urodyn 2005;24[5-6], 545-546..
Study 518	A multicenter, double-blind, randomized, placebo-controlled, parallel-group, study to explore the dose dependent response to three dose levels of BOTOX® (botulinum toxin type A) purified neurotoxin complex followed by an open label extension phase in patients with urinary incontinence due to neurogenic detrusor overactivity.	(191622-518)
Study 082	A placebo-controlled, randomized, safety and efficacy study of BOTOX® (botulinum toxin type A) purified neurotoxin complex in patients with neurogenic detrusor overactivity and neurological respiratory impairment.	(191622-082)
Study 094	Long-term extension trial of Study 515 and 516. A multicenter, long-term follow-up study of the safety and efficacy of two dose levels of BOTOX® (botulinum toxin type A) purified neurotoxin complex in patients with urinary incontinence due to neurogenic detrusor overactivity.	(191622-094)
Meta-analyses and systematic reviews		
Apostolidis A, et al	Recommendations on the use of botulinum toxin in the treatment of lower urinary tract disorders and pelvic floor dysfunctions: A European consensus report + Editorial	Eur Urol 2009;55(1):100-20.

Duthie J, et al	Botulinum toxin injections for adults with overactive bladder syndrome.	Cochrane Database Syst Rev 2007;(3):CD005493.
Karsenty G, et al	Botulinum toxin A (Botox(R)) intradetrusor injections in adults with neurogenic detrusor overactivity/neurogenic overactive bladder: A systematic literature review.	Eur Urol 2008;53(2):275-87.
Macdonald R, et al	Botulinum toxin for treatment of urinary incontinence due to detrusor overactivity: A systematic review of effectiveness and adverse effects.	Spinal Cord 2007;45(8):535-41.
Macdonald R, et al	Neurotoxin treatments for urinary incontinence in subjects with spinal cord injury or multiple sclerosis: A systematic review of effectiveness and adverse effects.	J Spinal Cord Med 2008;31(2):157-65.
Mangera A, et al	Contemporary management of lower urinary tract disease with botulinum toxin A: A systematic review of Botox (onabotulinumtoxinA) and Dysport (abobotulinumtoxinA).	Eur Urol 2011;44(2): 155-174.
Patel AK, et al	Botulinum toxin injections for neurogenic and idiopathic detrusor overactivity: A critical analysis of results + Commentaries.	Eur Urol 2006;50(4):684-710.
Ruffion A, et al	Botulinum toxin for neurogenic detrusor hyperactivity: Interest and results.	Pelv Perineol 2009;4(1):60-66.

8. Results of Trials

The results of the primary outcome, the change from baseline in weekly frequency of urinary incontinence (UI), from trials 515 and 516 at week 12 are presented below.

Trial ID	Botox 200 U			Placebo			Mean difference[a] (95% CI)
	N	Baseline	Δ	N	Baseline	Δ	
Week 12							
515	135	32.3±22.8	-20.8±22.4	149	28.3±15.8	-8.3±15.1	**-11.04 (-14.88, -7.19)**
516	92	32.5±18.4	-20.5±18.9	92	36.7±30.7	-12.2±22.2	**-8.86 (-4.51, -3.21)**
Pooled result 12 weeks							**-10.35 (-13.53, -7.17)**
Chi-square for heterogeneity: Chi^2 = 0.39 (*P=0.53)* I^2 statistic =0%							

Bold = statistically significant (p<0.05)

[a] mean difference between treatment groups (Botox – placebo) based on an ANCOVA model adjusted for baseline value, aetiology at study entry and investigator.

At week 12 Botox treatment resulted in a significantly greater reduction in weekly UI frequency compared to placebo. The pooled effect of Botox in trials 515 and 516 was -10.35 UI episodes/week (95% CI -13.53, -7.17). The submission stated that this was above the minimum clinical important difference (MCID) of three UI episodes/week. This MCID was not considered appropriate, as it was based on patients with overactive bladder syndrome, who would be expected to have lower UI episodes per week, compared to the patients included in the clinical trials.

The secondary outcome was the responder rate defined as a 50% reduction in weekly UI frequency. This was consistent with the requested listing, which requires a 50% improvement for continuation of treatment.

The results of reduction in weekly UI frequency (as responder and dry rates) of the pooled results of trials 515 and 516 at week 6 and 12 are shown below.

Reduction %	Botox 200 U n /N (%)	Placebo n /N (%)	Relative risk (95% CI)	Risk difference (95% CI)	NNT (95% CI)
At week 6					
50%	172/227 (75.8%)	93/241 (38.6%)	**1.96 (1.65 ,2.34)**	37.2 (28.9 ,45.5)	**2.7 (2.2 ,3.5)**
At week 12 [a]					
50%	172/223 (77.1%)	80/228 (35.1%)	**2.2 (1.82 ,2.66)**	42.0 (33.7 ,50.3)	**2.4 (2.0 ,3.0)**

NNT = number needed to treat

[a] While the submission states that all analyses were performed on an ITT basis, the results for these secondary outcomes included ongoing patients only.

At week 6 in the pooled data of trials 515 and 516, 75.8% of the patients in the Botox group achieved at least a 50% reduction in the number of UI episodes per week compared to 38.6% in the placebo arm, and 37% did not have any urinary incontinence compared to 9.1% in the placebo arm. These results were maintained at week 12.

For PBAC's view of these results, see Recommendation and Reasons.

Patients treated with Botox were more likely to have adverse events compared to the placebo group. These included treatment-related adverse events, urinary tract infections (UTIs), renal and urinary system, urinary retention, and treatment related to urinary retention.

The submission provided additional data on potential safety concerns beyond those identified in the clinical trials. Study 094 was the follow-up study for patients who completed trials 515 or 516 and did not have a study drug-related or study treatment-related serious adverse event. A total of 285 patients were enrolled with 146 assigned to Botox 200 U and 139 assigned to 300 U Botox. Most adverse events in treatment cycles 2 and 3 of trial 094 referred to urinary tract infection and renal and urinary disorders which were the main adverse events listed in the proposed PI. The PBAC considered that the adverse events associated with Botox for UI were consistent with the known safety profile of Botox.

9. Clinical Claim

The submission described Botox treatment as superior in terms of comparative effectiveness and inferior in terms of comparative safety over best supportive care.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a modelled economic evaluation based on the superiority claim for comparative benefit and the inferiority claim for comparative harms.

The submission used a semi-Markov model where the patients began therapy using either Botox or the comparator (BSC – placebo injections).

The submission noted that based on the reduction (%) at week 6 from baseline in urinary incontinence frequency, patients were assigned one of three health states:

- Dry: patients with 100% reduction in urinary incontinence frequency
- Responder: patients with a 50-99% reduction in UI frequency
- Non-responder: patients who fail to achieve even a 50% reduction in UI frequency.

Responders and dry patients could be re-treated with Botox or BSC. The submission noted that Botox will be equally effective in retreated patients as it was during the initial treatment. This was not appropriately modelled; patients who are re-treated (responders and dry) can only be dry or responder after re-treatment; the probability of being a non-responder after re-treatment equals 0. This favoured Botox.

The incremental cost per QALY of Botox treatment compared to best supportive care was between $15,000 - $45,000.

The results of the sensitivity analyses indicated that the model was most sensitive to the costs of continence products such as pads and catheters, and the probability of being dry, responder or non-responder after retreatment.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The net financial cost to the PBS was estimated to be less than $10 million in Year 5. The cost to the PBS was considered to be underestimated due to the omission of patients with NDO due to other causes, such as Parkinson disease and stroke as other populations were not specifically excluded in the proposed listing.

12. Recommendation and Reasons

The PBAC noted that evidence was presented for the use of botulinum toxin in patients with urinary incontinence (UI) due to neurogenic detrusor overactivity (NDO) in patients with multiple sclerosis (MS) and spinal cord injury (SCI). However, it was possible that botulinum toxin could be utilised for UI due to NDO in other patient groups including spina bifida, stroke and Parkinson disease. The PBAC noted that the requested restriction did not restrict treatment to MS and SCI patients and therefore use in other patient groups with UI due to NDO would be likely, although the PBAC considered that the number of patients with spina bifida was likely to be small and that while there may be some utilisation in Parkinson disease, the Committee noted that only some patients with Parkinson disease would be able to self-catheterise. The PBAC also noted that patients needed to have at least fourteen UI episodes per week to enter into trials 515 and 516, but the proposed PBS restriction did not include a definition of UI at baseline. Therefore the proposed PBS population could include patients with a reduced frequency of UI for which the efficacy of botulinum toxin is unknown.

The PBAC considered the comparator of best supportive care (BSC) was appropriate. BSC consists of non-pharmacological management such as lifestyle modification (e.g. moderating fluid intake, pre-emptive voiding, avoiding dietary bladder irritants), and the use of pads, portable urinals and clean intermittent catheterisation.

The PBAC considered that the evidence presented in the submission supported the claim of superior effectiveness of botulinum toxin over BSC in the treatment of UI due to NDO in patients with MS and SCI, although noting that the proposed PBS population may be wider than the patients represented in the trials. The PBAC noted that the adverse events associated with the use of botulinum toxin for UI due to NDO, including urinary tract infections and urinary retention, were consistent with the known safety profile of botulinum toxin and the PBAC agreed with the submission's claim that botulinum toxin is inferior to BSC in terms of comparative safety.

The PBAC considered that the incremental cost effectiveness ratio of botulinum toxin over BSC for the treatment of UI due to NDO was uncertain, but likely to be underestimated in the submission. The PBAC considered there were a number of areas of economic uncertainty which require clarification in order to more accurately ascertain the cost effectiveness of botulinum toxin in this condition. These include:

- The economic model presented in the submission was not transparent and hence the effect of adjusting some assumptions could not be evaluated.
- The PBAC noted that the model was sensitive to the cost of administration of botulinum toxin in NDO and that an application for a Medicare Benefits Schedule (MBS) item to administer botulinum toxin in NDO is currently under evaluation for the Medical Services Advisory Committee (MSAC). Therefore the PBAC sought advice from MSAC regarding the fee for administering botulinum toxin in the treatment of NDO in addition to the consultation fee likely required to assess and re-assess each patient, and the implications for out-of-pocket payments and the Extended Medicare Safety Net of medical practitioners charging patients more than the proposed MBS fee. The PBAC considered that the impact on the cost effectiveness of botulinum toxin in NDO of the cost of administration should be re-evaluated after the MSAC advice is available.
- The PBAC noted that the model was sensitive to the cost of continence products, such as pads and catheters, and considered that the cost of pads was overestimated in the submission. The PBAC considered that the assumption of a one to one reduction in voids to pad use may overestimate the extent of reduction in pad use as some patients may choose to continue to use pads.
- Both sets of utility values derived for use in the economic model are uncertain.

The PBAC considered the submission's utilisation estimates were uncertain, however underestimated as only patients with MS and SCI were included in the estimates, despite the proposed PBS restriction not limiting to these patient populations.

The PBAC hence deferred the submission, considering that the cost effectiveness was uncertain, and that the utilisation and financial estimates were uncertain. The PBAC considered that further information was required from MSAC regarding the cost of administration and monitoring and from the sponsor regarding the economic model and utilisation to inform a decision based on cost effectiveness.

The PBAC acknowledged and noted the consumer comments on this item.

Recommendation:
Defer

13. 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.

14. Sponsor's Comment

Allergan is committed to ensuring that patients suffering from urinary incontinence due to neurogenic detrusor overactivity get access to Botox® as soon as possible. Allergan is working with the PBAC and MSAC to ensure that a recommendation can be made at the earliest opportunity.