

PUBLIC SUMMARY DOCUMENT

Product: Botulinum toxin type A, 100 units injection, vial, Botox[®],

Sponsor: Allergan Pty Ltd

Date of PBAC Consideration: November 2013

1. Purpose of Application

The submission sought a Section 100 (Botulinum Toxin Program) Authority required listing for the treatment of urinary incontinence due to idiopathic overactive bladder (iOAB), in a patient who meets certain criteria.

2. Background

Botulinum toxin type A had not previously been considered by the PBAC for this indication.

3. Registration Status

Botulinum toxin type A was TGA registered for the treatment of overactive bladder with symptoms of urinary incontinence, urgency, and frequency, in adult patients who have an inadequate response to or are intolerant of an anticholinergic medication on 14 August 2013.

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 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.
- 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 equinus 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 idiopathic overactive bladder in patients who have ≥ 14 episodes/week, willing to self-catheterise, and have failed treatment with ≥ 2 anticholinergics.

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 6-12 weeks after the first treatment.

The PBAC noted that the requested restriction is consistent with the listing recommended in March 2013 for botulinum toxin in the treatment of urinary incontinence due to neurogenic detrusor overactivity (NDO). The PBAC also noted that the frequency of episodes (14 or more episodes/week) and number of anticholinergic agents a patient would be required to have failed under the proposed listing are not consistent with the inclusion criteria in the trials.

5. Clinical Place for the Proposed Therapy

Idiopathic overactive bladder is a clinical diagnosis characterised by the presence of symptoms of urinary dysfunction (e.g., a heightened sense of bladder fullness, increased bladder pressure, reduced storage volume, increased urinary frequency, and incontinence). The term 'idiopathic' is used when the pathology for the overactivity is not determined. This is in contrast to neurogenic detrusor overactivity, which results from a known underlying neurologic disorder (e.g., multiple sclerosis, spinal cord injury). Consequently, idiopathic overactive bladder is typically referred to as a 'diagnosis of exclusion', where all known causes of incontinence (e.g., urinary tract infection, diabetes insipidus, and bladder pain syndrome) have been ruled out.

Currently, treatment options for idiopathic overactive bladder 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. If these treatments are not effective, patients may be offered 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 urinary incontinence due to idiopathic overactive bladder, and who have failed conservative treatment (i.e., physiotherapy, behavioural therapy) and two lines of anticholinergic therapy, prior to the consideration of invasive surgical interventions.

The PBAC considered that the proposed patient population for the idiopathic overactive bladder was a much larger and less defined population compared to the NDO population.

6. Comparator

The submission nominated best supportive care (BSC) as the appropriate main comparator. BSC consists of non-pharmacological management such as lifestyle modifications, physiotherapy, and the use of continence aids (e.g., pads).

The PBAC accepted the nominated comparator as being appropriate.

7. Clinical Trials

The submission presented two phase III placebo-controlled double-blind trials (095 and 520) comparing botulinum toxin 100 U with placebo injection. All patients in the trials were able to access supportive non-pharmacological options (e.g., bladder training, lifestyle interventions), but not supportive pharmacological options (e.g., anticholinergic therapy) for their bladder symptoms. Overall, appropriate methods were followed in blinding, randomisation, concealment, follow up and handling missing data, indicating low risk of bias in these two pivotal trials. Longer term data are provided by the extension study of these trials (Study 096). Studies 095 (n=557) and 520 (n=549) were also used to inform the economic model presented. Both trials recruited patients with idiopathic overactive bladder with 3 or more urgency urinary incontinence episodes and 8 or more micturitions per day who were inadequately managed by at least one anticholinergic treatment. However, in the proposed restriction, patients have to fail at least two anticholinergic treatments.

The published trials and associated reports presented in the submission are shown in the following table:

Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
Study 095	Phase III multicentre, double-blind, randomized, placebo-controlled, parallel-group study of the safety and efficacy of a single treatment of Botox in iOAB patients with Urinary Incontinence. Nitti VW et al. Onabotulinumtoxin A for the Treatment of Patients with Overactive Bladder and Urinary Incontinence: Results of a Phase 3 Randomized Placebo-Controlled Trial. NCT00910845. Study of Botulinum toxin type A for the treatment of patients with idiopathic overactive bladder with urinary incontinence (http://ClinicalTrials.gov/show/NCT00910845).	The Journal of Urology. 2012.189:2186-2193.

Trial ID	Protocol title/ Publication title	Publication citation
Study 520	Phase III multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the safety and efficacy of a single treatment of Botox in iOAB patients with Urinary Incontinence Chapple C et al. OnabotulinumtoxinA 100 U Significantly Improves All Idiopathic Overactive Bladder Symptoms and Quality of Life in Patients with Overactive Bladder and Urinary Incontinence: A Randomised, Double-Blind, Placebo-Controlled Trial. NCT00910520. Botulinum toxin type A for the treatment of patients with idiopathic overactive bladder with urinary incontinence (http://ClinicalTrials.gov/show/NCT00910520).	European Journal of Urology. 2013. 64:249-256.

Supplementary randomised trials		
Study 077	Phase II multicenter, double-blind, randomised, placebo-controlled, dose-response study of the safety and efficacy of Botox in iOAB patients with urinary incontinence. Dmochowski R et al. Efficacy and safety of onabotulinumtoxinA for idiopathic overactive bladder: a double-blind, placebo controlled, randomized, dose ranging trial. Rovner E et al. Urodynamic results and clinical outcomes with intradetrusor injections of onabotulinumtoxinA in a randomized, placebo-controlled dose-finding study in idiopathic overactive bladder. Brubaker L et al. Treatment satisfaction and goal attainment with onabotulinumtoxinA in patients with incontinence due to idiopathic OAB. NCT00168454. A research study for patients with overactive bladder (http://ClinicalTrials.gov/show/NCT00168454).	2010. The Journal of Urology 184(6):2416-22. 2011. Neurourology and Urodynamics 30(4): 556-62. 2012. Int Urogynecol J 23(8):1017-25.
Study 096	A multicenter, long-term follow-up study of the safety and efficacy of Botox in iOAB patients with Urinary Incontinence NCT00915525. Long term follow-up study of safety and efficacy of Botulinum toxin type A for the treatment of patients with idiopathic overactive bladder with urinary incontinence (http://ClinicalTrials.gov/show/NCT00915525).	NA
Jabs 2010	Jabs C et al. Efficacy of botulinum toxin A intradetrusor injections for non-neurogenic urinary urge incontinence - a randomized double-blind control trial (Abstract number 296).	2010. Neurourology and Urodynamics. 29[6]:1228-1229.

iOAB= idiopathic overactive bladder; NA=not available

The sponsor requested a hearing for this item. The PBAC noted the perspective of the urogynaecologist's presentation in relation to impact on patients of urinary incontinence due to iOAB, current treatment guidelines, the administration procedure and other matters in response to the Committee's questions.

8. Results of Trials

With regard to comparative effectiveness, the co-primary outcomes in trials 095 and 520 were:

- 1) change from baseline in urinary incontinence episodes/day at Week 12; and
- 2) proportion of responders at Week 12 based on the Treatment Benefit Scale.

The results for change in urinary incontinence episodes per day at Week 12, are shown in the following table:

Change in urinary incontinence episodes per day at Week 12, mean (SD)

Trial	Botulinum toxin			Placebo			Mean difference (95% CI) ^a
	N	Baseline	Change week 12	N	Baseline	Change week 12	
095	280	5.5 (3.6)	-2.5 (3.4)	277	5.1 (3.2)	-0.9 (3.3)	-1.65 (-2.13, -1.17)
520	277	5.5 (3.8)	-3.0 (3.7)	271	5.7 (3.9)	-1.1 (3.8)	-1.91 (-2.43, -1.39)
Meta-analyses of the two trials (I ² = 0%)							-1.77 (-2.18, -1.35)

CI = confidence interval; SD = standard deviation.

^a The least square mean, p-values, between-group difference and its 95% CI are based on an analysis of covariance model.

The PBAC noted that treatment with botulinum toxin resulted in a statistically significantly larger reduction in urinary incontinence episodes per day compared to placebo in the two trials and in the pooled meta-analysis. The PBAC also noted that the reduction per week of 12.39 (1.77 X 7) is larger than the reduction previously considered by the PBAC to be clinically relevant (10.35 episodes per week at week 12) for patients treated for urinary incontinence due to neurogenic detrusor overactivity .

The PSD for the July 2012 meeting is available at the [PBS website](#).

The proportions of patients who achieved 50% or more (Responders) and 100% (Dry) reduction in urinary incontinence episodes/day at Week 12 in the pivotal trials are presented in the table below.

Proportion of patients achieving ≥ 50% and 100% reduction in urinary incontinence at Week 12

Trial ID	Botulinum toxin n/N (%)	Placebo n/N (%)	Botulinum toxin vs. Placebo		
			Risk difference (95% CI)	Relative risk (95% CI)	NNT ^a (95% CI)
≥ 50% reduction in urinary incontinence					
Study 520	176/277 (63.5)	90/271 (33.2)	0.30 (0.22, 0.38)	1.91 (1.58, 2.32)	3 (3, 5)
Study 095	161/280 (57.5)	80/277 (28.9)	0.29 (0.21, 0.36)	1.99 (1.61, 2.46)	3 (3, 5)
Meta-analysis results of pivotal trials (I ² = 0%)			0.29 (0.24, 0.35)	1.95 (1.69, 2.24)	3 (3, 4)
100% reduction in urinary incontinence					
Study 520	87/277 (31.4)	28/271 (10.3)	0.21 (0.15, 0.28)	3.04 (2.05, 4.50)	5 (4, 7)
Study 095	64/280 (22.9)	18/277 (6.5)	0.16 (0.11, 0.22)	3.52 (2.14, 5.78)	6 (5, 9)
Meta-analysis results of pivotal trials (I ² = 0%)			0.18 (0.14, 0.23)	3.22 (2.36, 4.37)	6 (4, 7)

^a Calculated during evaluation

CI=confidence interval; NNT=number needed to treat; **bold** = statistically significant (p<0.05)

The PBAC noted from the pooled results of the two pivotal trials, 60% of the patients in the botulinum toxin group achieved at least a 50% reduction in the number of urinary incontinence episodes per day compared to 31% in the placebo arm, and 27% achieved 100% reduction compared to 8% in the placebo arm at Week 12. Overall, the PBAC agreed that botulinum toxin is an effective treatment compared to BSC.

With regard to comparative harms, to assess the long-term safety and tolerability of botulinum toxin, patients who had completed trials 095 and 520 were included in the long-term follow-on study 096. The PBAC considered that the most common adverse events in repeated botulinum toxin courses were urinary tract infection and renal and urinary disorders, which is consistent with the reported events in the proposed product information (PI). The PBAC noted the additional safety data sourced from a literature review and the most recent periodic safety update report (PSUR); however, the PBAC noted that most of the data reported were from different doses and indications that are not consistent with the proposed listing.

The following table shows the proportion of patients developing the main adverse events in the clinical trials:

Proportion of patients developing the main adverse events in the clinical trials					
Trial ID	Botulinum toxin 100 U n/N (%)	Placebo n/N (%)	Botulinum toxin vs. Placebo		NNH (95% CI)
			Risk difference (95% CI)	Relative risk (95% CI)	
Urinary tract infection					
Study 520	56/274 (20.4)	14/270 (5.2)	0.15 (0.10, 0.21)	3.94 (2.25, 6.91)	6.6 (4.83, 10.2)
Study 095	43/278 (15.5)	16/272 (5.9)	0.10 (0.05, 0.15)	2.63 (0.08, 1.52)	10.4 (6.80, 22.2)
Pooled	99/552 (17.9)	30/542 (5.5)	0.12 (0.09, 0.16)	3.24 (2.19, 4.79)	8.1 (6.21, 11.5)
Urinary retention					
Study 520	16/274 (5.8)	1/270 (0.4)	0.06 (0.03, 0.08)	15.8 (2.11, 118)	18.3 (12.05, 38.5)
Study 095	15/278 (5.4)	1/272 (0.4)	0.05 (0.02, 0.08)	14.7 (1.95, 110)	19.9 (12.82, 43.5)
Pooled	31/552 (5.6)	2/542 (0.4)	0.05 (0.03, 0.07)	15.2 (3.66, 63.3)	19.1 (13.89, 30.3)
Catheterisation					
Study 520	19/274 (6.9)	2/270 (0.7)	0.06 (0.03, 0.09)	9.36 (2.20, 39.8)	16.2 (10.64, 33.3)
Study 095	17/278 (6.1)	0/272 (0.0)	0.06 (0.03, 0.09)	-	16.4 (11.24, 30.3)
Pooled	36/552 (6.5)	2/542 (0.4)	0.06 (0.04, 0.08)	17.67 (4.28, 73.0)	16.3 (12.05, 25.0)

NNH=number needed to harm, CI=confidence interval; **bold** = statistically significant (p<0.05)

The PBAC noted the numbers needed to harm (NNH) for common adverse events associated with botulinum toxin treatment are less than the numbers needed to treat (NNTs) for benefit. The PBAC noted that, consistent with the NDO restriction, willingness to self-catheterise is proposed as a requirement for eligibility under the proposed restriction. The PBAC considered this might assist in the management of treatment complications.

Overall, the PBAC agreed that botulinum toxin was associated with a higher rate of adverse events, particularly urinary tract infection and urinary retention, compared with placebo.

9. Clinical Claim

The submission described botulinum toxin treatment as superior in terms of comparative effectiveness and inferior in terms of comparative safety over BSC.

The PBAC considered this claim was reasonable based on the clinical evidence provided; however, the magnitude of benefits in the requested PBS population may be different from that reported in the pivotal trials because:

- BSC comprised supportive non-pharmacological options such as lifestyle modifications and physiotherapy, but not supportive pharmacological options such as anticholinergic therapy. Accordingly, it is possible that using outcome data from the clinical trials would overestimate botulinum toxin efficacy.
- The difference in inclusion and response criteria between the clinical trials and the proposed restriction, specifically patients needed to have failed one anticholinergic in the trial while they would need to fail two anticholinergic agents according to the proposed PBS restriction.

10. Economic Analysis

The submission presented a modelled cost utility analysis (CUA) of 10-year duration based on a superiority claim for comparative benefit and an inferiority claim for comparative harms. The modelled evaluation used a decision analytic Markov model to estimate the incremental cost-effectiveness of botulinum toxin compared to BSC in the treatment of idiopathic overactive bladder incontinence. In the model, patients treated with botulinum toxin are assessed 6-12 weeks post-treatment and categorised as either responders (achieving 50% or more reduction in the urinary incontinence episodes/day) or non-responders (achieving less than 50% reduction in urinary incontinence episodes/day).

Beyond 12 weeks, responders, non-responders and patients managed by best supportive care are progressed through the model in 3-month cycles. Patients are in one of the following health states in each 3-month cycle:

1. Dry (no incontinence episodes).
2. Responder 1 (50% or more reduction from baseline in average number of urinary incontinence episodes/day and 1 or less urinary incontinence episode/day).
3. Responder 2 (50% or more reduction from baseline in average number of urinary incontinence episodes/day and more than 1 urinary incontinence episode/day).
4. Non-responder (less than 50% reduction from baseline in average number of urinary incontinence episodes/day).
5. Dead (absorbing state in the model).

The PBAC noted the transformation issues, particularly the impact of using different methods to map quality of life data to utility values. Three different mapping approaches were used in the economic model. Incontinence Quality of Life (I-QOL) to Assessment of Quality of Life 8D Utility Instrument (AQoL-8D) was used in the base case while I-QOL to AQoL-8D using time trade off (TTO) and Short Form- 12 health survey (SF-12) to Short Form-6D health survey (SF-6D) were used in the sensitivity analyses.

To derive mapping from I-QOL to AqoL-8D, Richardson et al (2013) collected data from 177 Australian adults with at least one urinary incontinence episode per day. The PBAC noted that the algorithm was developed for the general population of overactive bladder urinary incontinence (including NDO) and was not specific for iOAB patients. The PBAC also noted the mapping was based on a relatively small sample size and there was poor correlation between the observed and predicted utilities.

For mapping I-QOL to AqoL-8D using TTO, a multi-attribute utility function for a reduced version of the I-QOL was estimated by eliciting preferences from a representative sample of the UK adult general population using visual analogue scale and time trade off rating exercises. The submission did not provide any details with regard to the algorithm used for the SF-12 to SF-6D mapping exercise.

The PBAC noted that the differences between utilities for the same health states derived using alternative approaches were in some cases bigger than the utility differences between the health states, suggesting considerable uncertainty regarding the appropriate utility values. The PBAC considered that the mapping approaches applied had many limitations and likely overestimated the utility gain from botulinum toxin.

The PBAC noted that the model used a disutility score of 0.25 for one day for the administration of botulinum toxin, but did not include disutilities for adverse events (e.g., UTI or catheterisation). The PBAC also noted that the model assumed 21% of patients would develop UTI during the first course of treatment based on the trial first cycle. The PBAC accepted this as being reasonable.

The PBAC noted that the base case utility values for the non-responder, responder and dry health states in the NDO submission were different from those in the idiopathic overactive bladder submission. The PBAC noted that it might be reasonable to expect that the utility gain from successful treatment in the idiopathic overactive bladder population may be greater than in the NDO population because the iOAB may be the key driver of quality of life reductions in the iOAB population, whereas the NDO population are likely to have limitations on role function (for example) even when incontinence is successfully managed. However, given the wide range of estimates of utility gains provided in the submission and the disparity with those for NDO, the PBAC was of the view that the submission's base case estimates likely overstated the utility gain.

The PBAC noted that the key drivers of the results of the economic evaluation are the cost of incontinence pads and that the submission uses differential prices (based on a survey of n=15 continence nurses requested to consider a total of 234 patients) across the health states (dry and responding states have lower pad prices than the non-responding state). The number of pads per day are also different between botulinum toxin and BSC arms; with pad usage increasing with the severity of patient's health state. The PBAC considered that this approach maximises the cost in non-responders and in BSC, both of which likely favour botulinum toxin.

The PBAC further noted that the differential pricing of pads for dry patients, for patients with one or less urinary incontinence episodes/day and patients with more than one urinary incontinence episodes/day was a different approach than PBAC had previously accepted for

the NDO submission wherein the price per pad was the same regardless of health state as well as the number of pads in each health state.

Furthermore, the PBAC noted the Economic Sub-Committee's (ESC) concern that the response rate for botulinum toxin may have been overestimated because the submission uses the results from the analysis of best response between weeks 6-12 in the clinical trial censoring non-assessed patients. The PBAC noted that the sponsor has addressed this in its Pre-PBAC response stating that the trial data were re-analysed and a sensitivity analysis was conducted where responders and non-responders are determined at the single time point of week 12. The results show that the cost savings would be greater and the quality adjusted life year (QALY) gain will be lower if the 12-week response was applied, and therefore the approach used in the submission did not favour botulinum toxin.

The PBAC noted that the base case analysis presented in the submission shows botulinum toxin to be dominant over BSC, with an incremental benefit and a reduced cost. From Step 2 of the stepped analysis applying the continuation rule to the trial-based analysis, the incremental cost per quality adjusted life years (QALY) is less than \$15,000 at 18 months. The PBAC noted that the economic evaluation is mainly driven by the cost offsets from the reduction in the use of incontinence pads and by the differences in utilities used across the health states.

The PBAC noted that the sensitivity analyses presented in the submission show that botulinum toxin is the dominant therapy in most instances. The PBAC also noted that the incremental cost effectiveness ratio (ICER) was sensitive to the cost of incontinence pads, quality of life scores and retreatment rate. The Pre-Subcommittee response provided additional sensitivity analyses, including multivariate sensitivity analyses. The PBAC noted that the most conservative of these multivariate sensitivity analyses increased the ICER to less than \$15,000/QALY over 10 years.

Additionally, the PBAC noted the most conservative multivariate sensitivity analysis provided in the evaluation resulted in an ICER of between \$15,000-45,000. The PBAC noted that this ICER was in the range of the corresponding ICERs from the NDO submission.

The PBAC considered the effect of the uncertainties in the model particularly the varying cost and use of pads per health states, the utility values, the non-inclusion of the cost of antibiotic prophylaxis during the cystourethroscopy procedure and the cost of catheterisation. The PBAC agreed that these should be factored into the total cost of botulinum toxin treatment. The PBAC noted the ICER of between \$15,000-45,000/QALY probably reflected a worst case scenario, and considered that a lower ICER (but within the same range) to be a more plausible estimate.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year who would receive botulinum toxin was estimated by the submission to be between 100,000 and 200,000 in Year 5.

This only reflects patients with idiopathic overactive bladder, as this indication does not cover urinary incontinence due to neurogenic detrusor overactivity or patients with stress

incontinence. The PBAC noted the Drug Utilisation Sub-Committee (DUSC) advice that the number of potentially eligible patients was likely to be underestimated due to imprecision in establishing the diagnosis and in establishing failure to prior anticholinergic agents. However, the PBAC also accepted DUSC advice that the actual uptake may be less than the usage estimates because it is likely to be limited by patient willingness to self-catheterise, access to specialists and hospital clinic capacity.

The submission estimated that the net cost over the first 5 years to subsidise botulinum toxin for idiopathic overactive bladder incontinence is greater than \$50 million for the PBS and greater than \$100 million for the Government (both PBS and MBS).

The PBAC noted that the sponsor provided details of a proposed risk share arrangement (RSA) to reduce uncertainty with regard to utilisation estimates and cost of botulinum toxin to the PBS. Given the PBAC's concerns about the likelihood of the estimated ICER being reflected in practice, the expected difficulty in differentiating use within and beyond the intent of the restriction, and the uncertainty in the estimated PBS usage and financial implications, the Committee considered that a tighter RSA would be required than that offered in the re-submission with a larger rebate being payable for exceeding the subsidisation cap.

12. Recommendation and Reasons

The PBAC recommended extending the listing of botulinum toxin in the PBS via the Section 100 Botulinum Toxin Program to include treatment of urinary incontinence due to idiopathic overactive bladder in a patient who meets certain criteria, on the basis of acceptable cost-effectiveness compared to best supportive care. To address the uncertainty in the cost-effectiveness being reflected in practice, the PBAC recommended that a tighter risk share arrangement be negotiated with the sponsor, with larger rebates and caps based on the smaller estimates of use provided in the submission.

The PBAC acknowledged that a clinical need exists for an effective treatment of patients with idiopathic overactive bladder. The PBAC noted the advice from the Urological Society of Australia supporting the application and suggesting that best supportive care remains the first option for treatment for idiopathic overactive bladder and that botulinum toxin is placed in the treatment algorithm in between anticholinergic treatment and more invasive therapies such as sacral nerve stimulation.

The PBAC accepted best supportive care as the appropriate comparator.

The PBAC accepted that the results of trials 095 and 520 supported the claim of superior comparative efficacy and inferior comparative safety of botulinum toxin over best supportive care.

The PBAC considered the most conservative ICER of between \$15,000-45,000/QALY presented in the sensitivity analyses may overestimate the true ICER of botulinum treatment in clinical practice, given difficulties in addressing a number of issues with the economic evaluation including the transformation issues particularly the utility values and the varying cost and use of incontinence pads over different health states. However, the PBAC also

considered that the non-inclusion of the cost of antibiotic prophylaxis during cystourethroscopy, the cost of catheterisation, and the expected difficulty in differentiating use within and beyond the intent of the restriction all contribute to an underestimate in this sensitivity analysis. On balance, the PBAC considered a lower ICER (but within the same range) to be a more plausible estimate.

The PBAC noted the submission’s estimates of patients treated, botulinum treatment costs, antibiotic costs for treatment of UTI and net costs to the PBS/MBS were underestimated likely due to underestimation of patient numbers and potential under-estimation of other costs. The PBAC considered that the cost of antibiotic prophylaxis during cystourethroscopy and the cost (i.e. potential harm) of self-catheterisation should be factored into the total cost of botulinum toxin treatment.

The PBAC noted and welcomed the input received from individuals (37), health care professionals (4) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with botulinum toxin including ability to function normally/return to work, relief from anxiety and embarrassment, reduced costs (pads, laundry) and fewer side effects from other medicines.

The Safety Net 20 Day Rule should not apply.

The PBAC considered that botulinum toxin remains unsuitable for inclusion in the list of PBS medicines for prescribing by nurse practitioners.

Recommendation:

Recommended

Extend the current listing for botulinum toxin to include the following.

Name, Restriction, Manner of administration and form	Pack size	Proprietary Name and Manufacturer	
BOTULINUM TOXIN TYPE A Botulinum toxin type 1 100 units injection, 1 x 100 units vial	1	Botox	AG

Condition:	Urinary incontinence
Restriction:	Section 100 Botulinum Toxin Program

Clinical criteria:	<p>The condition must be due to idiopathic overactive bladder</p> <p>AND</p> <p>The condition must have been inadequately controlled by therapy involving at least two alternative anti-cholinergic agents</p> <p>AND</p> <p>Patient must experience at least 14 episodes of urinary incontinence per week prior to commencement of treatment with botulinum toxin</p> <p>AND</p> <p>The treatment must not continue if the patient does not achieve a 50% or greater reduction from baseline in urinary incontinence episodes 6-12 weeks after the first treatment.</p>
Population criteria:	Patient must be aged 18 years or older.
Population criteria:	Patient must be willing and able to self-catheterise.
Administrative Advice	Special Pricing Arrangements apply

It was noted that the Sponsor's submission had requested a population criterion in the proposed restriction that the patient must be an adult, consistent with the TGA approved indication for botulinum toxin in iOAB. The PBAC recommended at the November 2013 PBAC meeting to include a population criterion stating "Patient must be aged 18 years or older", for consistency with the sponsor's request, the TGA approved indication and the trial data presented in the submission.

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

The sponsor has no comment.