PUBLIC SUMMARY DOCUMENT
Product: Botulinum Toxin Type A Purified Neurotoxin Complex, lyophilised powder for I.M. injection 100 units vial, Botox®
Sponsor: Allergan Australia Pty Ltd
Date of PBAC Consideration: November 2008

1. Purpose of Application

The submission sought to extend the Section 100 (Botulinum Toxin Program) listing for botulinum toxin type A to include treatment of moderate to severe spasticity of the upper limbs of children (2 years of age or older) with cerebral palsy.

2. Background

Botulinum toxin type A was first listed on the PBS under Section 100 (Botulinum Toxin Program) in October 1994 for the treatment of blepharospasm associated with dystonia, including benign blepharospasm and VIIth nerve disorders (hemifacial spasm) in patients 12 years and older. At the December 1999 meeting, the PBAC recommended extension of the Section 100 listing to include the treatment of dynamic equinus foot deformity due to spasticity in juvenile cerebral palsy patients two years of age and older, on the basis of acceptable cost-effectiveness.

At the March 2001 meeting, the PBAC recommended further extending the listing to include treatment of spasmodic torticollis, either as monotherapy or as adjunctive therapy to current standard care on a cost-minimisation basis compared with clostridium botulinum type A toxin (Dysport®).

At the November 2005 PBAC meeting, the Committee rejected an application to extend listing to include the treatment of focal spasticity in adults because of uncertainty with interpreting the extent of clinically relevant benefits arising from the spasticity outcomes analysed by the trials, uncertainty associated with the modelled physiotherapy cost off-sets, and the resulting unacceptable and uncertain cost-effectiveness (See also Public Summary Document of November 2005).

In July 2006, the PBAC again rejected a submission seeking listing for the treatment of focal spasticity of upper and lower limbs in adult patients who meet certain criteria based on high and uncertain cost-effectiveness (See also Public Summary Document of July 2006).

At the July 2008 meeting, the PBAC recommended an extension to the Section 100 listing for Botulinum toxin type A to include the treatment of moderate to severe spasticity of the upper limb in adults following a stroke, as second line therapy when standard management has failed or as an adjunct to physical therapy, on a cost-minimisation basis compared with clostridium botulinum. At the same meeting the PBAC rejected a submission requesting extension of the current section 100 listing to include the treatment of moderate to severe spasticity of the lower limb in ambulatory adults following a stroke as a second line therapy when standard management has failed or as an adjunct to physical therapy because of uncertain clinical benefit and the resulting high and uncertain cost-effectiveness (See also Public Summary Document of July 2008).

3. Registration Status

Botulinum toxin type A was first registered by the TGA on 9 September 1999. It is indicated for:

- Treatment of blepharospasm associated with dystonia, including benign blepharospasm and VVI nerve disorders (specifically hemifacial spasm) in patients twelve years and over;
- Treatment of cervical dystonia (spasmodic torticollis);
- Treatment of dynamic equinus foot deformity due to spasticity in juvenile cerebral palsy patients two years of age or older;
- Treatment of severe primary hyperhidrosis of the axillae;
- Treatment of glabellar lines associated with corrugator and/or procerus muscle activity;
- Treatment of focal spasticity in adults;
- Treatment of spasmodic dysphonia, and treatment of strabismus in children and adults;
- **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.**

4. Listing Requested and PBAC's View

The sponsor proposed two alternative listings. The first used improvements in the Goal Attainment Scaling (GAS) as a continuation criterion and was the sponsor's preferred option. The second listing used a 10 % improvement in the Quality of Upper Extremity Skills Test (QUEST) as a continuation criterion.

First proposed listing:

Section 100 (Botulinum Toxin Program)
Treatment of moderate to severe spasticity of the upper limbs of children (2 years of age or older) with cerebral palsy.

Initial treatment

To be eligible for treatment patients must have an Ashworth score of at least 2 in the affected muscle. At the start of treatment the patient must be assessed and 3 or more treatment goals identified consistent with Goal Attainment Scaling.

Continuing Treatment

Patients should be considered eligible for re-treatment after at least 4 months have elapsed since their previous treatment. Patients are only eligible for re-treatment if they have, on average, achieved their treatment goals identified at baseline (i.e. have achieved an average T-score > 50 in GAS score at follow-up). Patients that have responded to therapy after initial treatment are eligible for subsequent treatments that in the judgement of the treating clinician continue to provide a clinical benefit.

Second proposed listing:

Section 100 (Botulinum Toxin Program)
Treatment of moderate to severe spasticity of the upper limbs of children (2 years of age or older) with cerebral palsy.

Initial treatment

To be eligible for treatment patients must have an Ashworth score of at least 2 in the affected muscle. At the start of treatment the patient must be assessed using the Quality of Upper

Extremity Skills Test (QUEST) to determine their baseline value. The score will be used to determine whether the patient should be re-treated in the future.

Continuing Treatment

Patients should be considered eligible for re-treatment after at least 4 months have elapsed since their previous treatment. Patients are only eligible for re-treatment if they have improved by = 10 points on the QUEST total score from their initial or baseline assessment. Patients that have responded to therapy after initial treatment of eligible for subsequent treatments that in the judgement of the treating clinician continue to provide a clinical benefit.

For PBAC's view see Recommendation and reasons.

5. Clinical Place for the Proposed Therapy

In the treatment of upper limb spasticity in children, botulinum toxin type A produces a reduction in muscle tone, increased range of motion, reduced pain and reduced spasticity-related functional disability.

6. Comparator

The submission nominated standard management as the main comparator. Standard management in the submission was considered to be physical and/or occupational therapy.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The basis of the submission was six direct randomised comparative trials and two supplementary randomised comparative trials comparing botulinum toxin type A (BTx-A) and standard management.

A list of the six direct randomised comparative trials that were published at the time of the submission is presented in the table below.

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
Lowe K et al, 2006	Low-dose/high-concentration localized botulinum toxin A improves upper limb movement and function in children with hemiplegic cerebral palsy.	Developmental Medicine and Child Neurology 2006 Mar;48:170-5.
Boyd RN et al, 2006	A randomized trial of botulinum toxin A and upper limb training in congenital hemiplegia: outcomes of activity, participation and societal change.	Dev Med Child Neurol 2003; 45(Suppl 94):49
Wallen M et al, 2007	Functional outcomes of intramuscular botulinum toxin type A and occupational therapy in the upper limbs of children with cerebral palsy: A randomized controlled trial.	Arch Phys Med Rehabil 2007;88(1):1-10.
Speth LA et al, 2005	Botulinum toxin A and upper limb functional skills in hemiparetic	Developmental Medicine And Child Neurology 2005 Jul;47:468-73

	cerebral palsy: a randomized trial in children receiving intensive therapy.	
Fehlings D et al, 2000	An evaluation of botulinum -A toxin injections to improve upper extremity function in children with hemiplegic cerebral palsy	The Journal of Pediatrics 2000 Sep;137:331-7.
Russo RN et al, 2007	Upper limb botulinum toxin A injection and occupational therapy in children with hemiplegic cerebral palsy identified from a population register: a single blind randomised trial.	Pediatrics 119 (5):e1149-58.

8. Results of Trials

The primary efficacy analysis in the submission was based on analyses of three of these six trials; Lowe (2006), Wallen (2007), and Fehlings (2000). The submission stated that only these studies provided data that was sufficient to derive a responder analysis. The efficacy analysis was based on two outcomes: Goal Attainment Scale (GAS) and the Quality of Upper Extremity Skills Test (QUEST), which the submission justified as being the most appropriate outcomes for measuring efficacy, and were also proposed as the basis of continuation criteria in the two alternative PBS listings. GAS assessed patient performance based on pre-specified patient goals whilst QUEST provided a comprehensive assessment of four domains, dissociated movement, grasp, weight bearing and protective extension. QUEST was the primary outcome in trials Lowe (2006) and Fehlings (2000), whilst GAS was the primary outcome in Wallen (2007) and a secondary outcome in Lowe (2006).

As the individual studies had different primary endpoints, which were not reported consistently across trials, the submission presented only a summary of results for each trial. There was a statistically significant difference in QUEST scores favouring BTx-A in Lowe (2006) and Fehlings (2000) at one month, but not at six months. There was no statistical significance difference in QUEST scores in Wallen (2007) between treatments. Similarly, there was no statistical significant difference in GAS scores between treatment arms in Boyd (2006), Wallen (2007) and Russo (2007). Based on the functional outcome measures used in the six trials, efficacy of BTx-A remained uncertain.

The primary efficacy analysis in the submission was based on a post hoc responder analysis of the QUEST and GAS outcomes. There was a statistically significant difference in the number of subjects with $\geq$ 10 point improvement in QUEST score (based on two domains) favouring BTx-A in the Lowe (2006) trial at 4 and 12 weeks but not at 26 weeks. A similar level of response was observed in the study by Fehlings (2000).

For the GAS responder analysis, there was a statistically significant difference in the number of subjects achieving goals favouring BTx-A in the Lowe (2006) trial at 4 weeks but not at 12 or 26 weeks. There was no statistically significant difference in the number of subjects achieving goals between treatments for Wallen (2007) at either 12 or 26 weeks.

The submission performed analysis based on scores derived from therapist ratings rather than parent ratings. The submission did not provide any justification for using scores based on therapy ratings only, however it was noted that therapists (outcome assessors) were blinded to treatment, while parents were not. During the evaluation analysis on the parent scores, based

on trial data from Lowe (2006) showed no statistically significant difference in the number of subjects achieving goals between the BTx-A plus therapy arm versus the therapy alone arm at any of the assessment weeks.

The submission conducted an additional responder analysis based on data from Lowe 2006. The revised analysis was based on a responder definition of > 50 points on the GAS and 20 % improvement from baseline. The submission states this was performed as it was identified that there were large differences between the treatment arms in the change from baseline for mean GAS scores. The submission did not justify the use of this responder definition on the basis of any published sources.

There was a statistically significant difference between treatments in the number of subjects with > 50 points on the GAS and 20 % improvement from baseline favouring BTx-A at all the assessment points. An updated analysis conducted during the evaluation found the difference was significant at 4 weeks but not at 12 or 24 weeks.

The re-submission presented toxicity data based on clinical trials in upper and lower limbs, and data from post marketing surveillance.

Adverse events reported by Lowe 2006

Adverse events	BTx-A N = 21 n(%)	Control N = 21 n(%)
Any serious adverse event	1 (4.8%)	2 (9.5%)
Any serious adverse event related to drug treatment	0	0
Any adverse event	10 (48%)	5 (24%)
Discontinuations due to adverse event	0	0

The submission stated that on the basis of clinical trial data and post marketing surveillance data adverse events to BTx-A were mild and not treatment limiting. The additional safety data provided in the submission was primarily based on BTx-A use in lower limbs. Safety data pertaining to upper limbs were limited.

The submission did not provide safety data on the potential effects of cumulative dosing in patients receiving multiple muscle treatment, for example if they are having treatment for both upper and lower limb spasticity. During the evaluation a literature search identified a retrospective study which used BTx-A in multiple muscles in children with cerebral palsy (Heinen et al 2006)[1]. The percentage of sessions with adverse events was 22.2 % when the number of muscles injected were between 12 and 19 compared to 9 % when number of muscles injected < 8.

9. Clinical Claim

The submission described BTx-A as superior in terms of comparative effectiveness and inferior/uncertain in terms of comparative safety over standard management for the treatment of juvenile cerebral palsy.

For PBAC's view see Recommendation and Reasons.

[1] Heinen F, Schroeder AS, Fietzek U, Berweck S. When it comes to botulinum toxin, children and adults are not the same: multimuscle option for children with cerebral palsy. *Mov Disord.* 2006 Nov; 21(11):2029-30.

10. Economic Analysis

A trial based economic evaluation was presented.

A cost effectiveness analysis based on following two responder definitions was presented:

- QUEST - patients achieving a ≥ 10-point improvement in QUEST score; the incremental cost effectiveness ratio (ICER) was < $15,000 either following single injection or at one year; and
- GAS - patients who have achieved their treatment goal (GAS score > 50 and 20 % improvement from baseline); the ICER was < $15,000 either following single injection or at one year.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of patients per year was < 10,000, while the financial cost per year to the PBS was estimated to be < $10 million in year five. The submission's estimates were uncertain. Details of calculations to determine the number of patients eligible for treatment and total treatment cycles in a year were not provided. The submission also did not calculate the monitoring costs of BTx-A administration which was not appropriate as under the Botulinum toxin program the patient has to receive BTx-A from a specialist. Sensitivity analyses performed during evaluation indicated that the financial estimates were sensitive to the responder definition based on the GAS score (GAS >50 or GAS score >50 and 20% improvement from baseline) and the number of vials in the treatment cycle.

12. Recommendation and Reasons

The PBAC recommended extending the availability of botulinum toxin type A through the Section 100 Botox program to include the treatment of moderate to severe spasticity of the upper limb(s) in cerebral palsy patients aged 2 years and over on the basis of acceptable cost effectiveness in the context of a condition in which large utility gains are probable in responders to treatment, and where non-responders are unlikely to continue treatment.

The PBAC accepted the clarification provided by the sponsor in the pre-Sub-Committee response that the intent of the submission was to demonstrate the cost-effectiveness of botulinum treatment based on the outcome of T-score greater than or equal to 50 in Goal Attainment Scaling (GAS) score at follow-up and a 20 point absolute improvement in the score from baseline, rather than a 20 % improvement from baseline as originally appeared in the submission. Based on this definition of response, the pivotal trial (Lowe 2006) demonstrated that a statistically significant greater number of children treated with botulinum achieve a response in comparison with patients in the placebo arm. In addition, the trial demonstrated that the difference between the treatment and comparator arms remains statistically significant at 4, 12 and 26 weeks, although the absolute benefit of treatment decreases over time, which is consistent with the literature in this field.

However, the Committee noted that this conclusion is associated with some uncertainty in relation to the precise extent of the treatment benefit achieved with botulinum treatment because the responder analysis was post-hoc and the GAS scores as rated by the therapist were consistently higher than the GAS scores as rated by the parents. In addition, the PBAC also noted that the results of the other five randomised trials included in the submission did not uniformly demonstrate a benefit for botulinum treatment in comparison with standard management in children with cerebral palsy with moderate to severe focal spasticity of the upper limb.

The hearing confirmed that treatment of children with focal spasticity involves goals setting as agreed between the parents and physicians, followed by a review at one month, and then assessment of adverse events and re-treatment as required at four - six months, although the Goal Attainment Scaling is not routinely used in current clinical practice. Therefore, the PBAC did not consider that the inclusion of the Goal Attainment Scaling as part of the PBS restriction was useful in clinical practice, and was also reassured that the use of botulinum in this indication was unlikely to be abused. In addition, the continuation rule proposed by the submission was not considered to be informative for the purpose of maintaining the cost-effectiveness of botulinum in this indication. Therefore the PBAC recommended that the restriction should be simplified to "moderate to severe spasticity of the upper limbs in a cerebral palsy patient (2 years or older)" with continuing treatment to be allowed in patients who achieve a response.

The PBAC noted that the economic evaluation was a cost-effectiveness evaluation which calculated a cost per responder only, but the hearing provided adequate details of the meaning of this outcome for patients which meant that the result of the economic analysis could be interpreted by the Committee who considered it likely to translate into a reasonable cost per Quality Adjusted Life Year gained.

The PBAC noted that the hearing stated that based on the results of an audit conducted in 274 patients the mean dose/kg was 11.3 Unit (range 0.9-19.4 Units/ kg) which was higher than the average botulinum dose of 155 units per patient used in the clinical trials. Therefore, the Committee recommended that treatment be limited to a maximum of 2 vials/ cycle, no more often than twice a year.

The PBAC also recommend that children who have been treated with Dysport for upper limb spasticity should be able to access Botox once it becomes PBS listed. Patients who commenced PBS-subsidised treatment for this condition before their eighteenth birthday should be permitted to continue treatment in adulthood.

Recommendation
BOTULINUM TOXIN TYPE A PURIFIED NEUROTOXIN COMPLEX, lyophilised powder for I.M. injection 100 units vial, Botox®

Amend the current restriction by adding:

Section 100 (Botulinum toxin program)
Treatment of moderate to severe spasticity of the upper limbs in a cerebral palsy patient 2 years of age or older.

Pack size: 1

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 welcomes the decision of the PBAC and believes that Botox® will provide a valuable treatment option for patients with cerebral palsy.