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: July 2006

1. Purpose of Application

The submission requested an extension to the Section 100 listing (under the Botulinum Toxin Program) for botulinum toxin type A to include the treatment of focal spasticity in adults.

2. Background

At the November 2005 PBAC meeting the Committee rejected an application to extend the Section 100 listing for botulinum toxin type A to include the treatment of focal spasticity in adults.

The PBAC rejected the submission 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.

3. Registration Status

Botulinum Toxin Type A Purified Neurotoxin Complex is indicated for:

- Treatment of blepharospasm associated with dystonia, including benign blepharospasm and VII 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;
- Treatment of strabismus in children and adults.

4. Listing Requested and PBAC's View

Section 100
Botulinum Toxin Program
For the treatment of focal spasticity in adult patients in cases when
(a) there is no fixed muscle contracture to limit treatment efficacy
(b) non-invasive treatments (physical therapies) have failed
(c) treatment is in conjunction with a therapy program designed to meet defined functional goal(s) of treatment.

Treatment is indicated in patients who have functional disability due to focal spasticity in the upper or lower limb and who have failed other treatments. In the lower limb the use of BOTOX® is clinically indicated to facilitate the use of an orthosis (such as an ankle-foot orthosis [AFO]); improve the placement of the foot surface against the ground surface such as in the correction of equinus gait or flexor spasms of the toes; treat spasticity causing significant hygiene problems and limiting independent transfers (such as hip adductor and hamstring spasticity); achieve a significant change in gait speed; or reduce the need for mobility aids.
Treatment of the upper limb is indicated in patients who have localised pain due to overactive muscle activity of spasticity; need improvements in grasp and release (required for the use of mobility aids and daily activities such as feeding or self-care); or who have failed to be effectively treated for focal spasticity causing medically significant hygiene issues).

A sustained therapy program may include physiotherapy, occupational therapy or a self- or carer-administered physical program. Physical therapy is considered to have failed when patients are unable to achieve targeted functional goals.

Treatment is limited to two injections in the first year and, if necessary to maintain functional goals, one injection per year in the second and subsequent years.

The PBAC's view was that it would be appropriate to limit the number of treatment doses per patient and that, were listing recommended, general physicians and geriatricians with the appropriate training could be permitted to use botulinum toxin.

5. Clinical place for the proposed therapy

Botulinum Toxin Type A (BTx-A) injection therapy treats spasticity by allowing the muscle to relax. The effects of Botulinum Toxin Type A are reversible and treatment provides a window of opportunity in which other treatments, such as physical therapies, can be used to regain muscle or joint function.

6. Comparator

Placebo for standard medical management. This was as previously agreed by the PBAC.

7. Clinical Trials

No changes were made to the trial data presented in the previous submission. The trials published at the times of the submission were:

Trial/First author	Protocol/Publication title	Publication citation
191622-008/ Brashear A et al.	Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke.	New England Journal of Medicine 2002;347:395–400
Brashear A et al	A multicenter, double-blind, randomized, placebo-controlled, parallel study of the safety and efficacy of BOTOX® (botulinum toxin type A) purified neurotoxin in the treatment of focal upper	American Academy of Neurology 53rd Annual Meeting. Neurology 2001; 56:8(Suppl 3); A78

Trial/First author	Protocol/Publication title	Publication citation
	limb spasticity post-stroke.	
130-8051/ Simpson DM et al. O'Brien CF et al.	Botulinum toxin type A in the treatment of upper extremity spasticity: a randomised, double-blind, placebo-controlled trial. A randomised, double-blind, placebo-controlled study to evaluate the use of botulinum toxin type A in the treatment of spasticity	Neurology 1996: 46:1306–10 Neurology 1995; 45(Suppl 4):A329
133/134-8051/ Childers MK et al. Childers MK et al	A multicenter, double-blind, placebo-controlled dose response trial of botulinum toxin type A (BOTOX® in upper limb spasticity post-stroke. Dose-dependent response to intramuscular botulinum toxin type A for upper-limb spasticity in patients after a stroke.	Neurology 1999;52:A295 Archives of Physical Medicine and Rehabilitation 2004; 85:1063–9
418/422-8051/ De Beyl Z et al	A multicenter, double-blind, placebo-controlled trial to evaluate dosing, safety and efficacy of intramuscular botulinum toxin type A for the management of upper limb spasticity poststroke.	European Journal of Neurology 2000;7(Suppl 3):23
702-8051/ Dunne J.	Botulinum toxin type A BOTOX® in the treatment of lower limb spasticity during stroke rehabilitation	Internal Medicine Journal 2003;33:A41
Verplancke et al (with no new data available)	A randomized controlled trial of botulinum toxin on lower limb spasticity following acute acquired severe brain injury.	Clinical Rehabilitation 2005; 19(2): 117-125.

8. Results of Trials

The re-submission re-ran the post hoc Ashworth scale responder analysis based on a revised responder definition as a patient with a reduction of ≥2 points in the tonicity in at least one injected muscle.

Walking speed and endurance, secondary outcomes in Trial 702-8051, were further analysed. Significant improvements were found in BTx-A patients who were unable to function normally at baseline. However, patients were selected by functional deficit and there appeared to be more disabilities in the placebo group at baseline. The numbers achieving improvements in clinically significant measures, eg. ability to walk 10m in 12.5 secs and ability to walk 332 m, were not reported. Disability Assessment Scale (DAS) analyses for the selected principal therapeutic target and all four targets on patients with baseline disability in that domain, showed patients benefited significantly more from BTx-A treatment than placebo. However, statistically significant improvements in all DAS domains were only evident when 1-point reduction in the DAS was measured as outcome. The numbers of patients requiring permanent treatment were not reported.

The resubmission provided the results for each domain of the DAS for Trial 191622-008, which showed that at Week 6, significant improvements from baseline were identified in principal therapeutic targets of limb positioning and hygiene in BTx-A group, while no significant difference was shown in dressing or pain between treatments. At Week 12, most of the domains failed to show any significant difference between treatments except for the limb positioning component.

No new toxicity data were presented in the re-submission.

9. Clinical Claim

The submission claimed BTx-A has significant advantages in effectiveness over placebo and has similar toxicity. The PBAC, on balance, accepted that a 2 point reduction in the Ashworth scale was clinically relevant.

10. Economic Analysis

An updated preliminary economic evaluation was not presented in the submission, but was conducted during the evaluation. The trial-based incremental cost per extra patient achieving ≥ 2-point reduction in the Ashworth (or expanded Ashworth) scale in at least one injected muscle was estimated to be < $15,000.

An updated modelled economic evaluation was presented. A cost-utility approach was employed in the re-submission compared to a cost-effectiveness model in the previous submission. However, the way of mapping Ashworth scores to health states may have failed to capture the important underlying causes of focal spasticity and clinical conditions.

The base case modelled incremental discounted cost per extra discounted QALY gained was estimated to be in the range of $15,000 - $45,000 in the submission. However, in the calculation of QALY gains for non-responders in both BTx-A and placebo groups, QALY gains in lower limb were omitted which meant that QALYs gained in the placebo arm were under-estimated.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated to be up < 10,000 in Year 4, while the financial cost per year to the PBS was estimated to be < $10 million in Year 4.

12. Recommendation and Reasons

The PBAC noted the re-submission clearly defined the target patient population, and considered that it would be appropriate to limit the number of treatment doses per patient. The PBAC considered that were listing recommended general physicians and geriatricians with the appropriate training could be permitted to use botulinum toxin.

The PBAC noted ESC advice that the key clinical issue remained whether a 1-point reduction in the Disability Assessment Scale (DAS) or 2 point reduction in the Ashworth scale is clinically important and patient relevant. The PBAC was informed during the hearing and also noted that the Expert Panel Consensus Statement states that a 2-point change in the Ashworth score is associated with improvement of limb function and hygiene. On balance the Committee thus accepted that this change was clinically relevant.

There was less certainty about the interpretation of a 1 point change in the DAS. The DAS analyses for the selected principal therapeutic target and all four targets on patients with baseline disability in that domain, showed patients benefited significantly more from

BTx-A treatment than placebo. However, statistically significant improvements in all DAS domains were only evident when 1-point reduction in the DAS was measured as the outcome. Further, the clinical outcome measured in the DAS varied from patient to patient and therefore it was difficult to place a consistent value on a 1 point reduction in this scale. The PBAC noted that in Trial 1961622-008 at week 6, the risk difference showed a statistically significant improvement over the total of the domains, however, at week 12 statistically significant improvement was shown only in limb positioning.

The PBAC also noted there was uncertainty regarding the duration of the effectiveness of treatment as the numbers requiring permanent treatment were not reported.

The PBAC considered the major uncertainty of the submission was the utility study using an AQoL survey, which mapped Ashworth scores to health states. The PBAC considered that this approach failed to capture the underlying varied causes of focal spasticity and the complexity of the clinical conditions.

The PBAC considered the method for estimating utilities to be flawed. Some of the reasons are:

- a 2-point reduction in the Ashworth score cannot be assumed to give a consistent increase in utility across all ranges of scores. The Ashworth scale is a five-point scale detailed as follows: 0 = no increase in tone; 1= slight increase in tone, giving a catch when the limb is moved in flexion or extension; 2=more marked increase in tone but limb easily flexed; 3= considerable increase in tone – passive movement difficult; 4=limb rigid in flexion or extension;
- the results do not appear to be plausible. For example, a utility gain of 0.254 for an upper limb non-responder (scenario C), which was noted in the Pre-PBAC Response to correspond to a 1-point improvement on the Ashworth score, implies that a person is prepared to give up more than a quarter of the life expectancy for the relevant time period just to try therapy with BTx-A.

Further, the sensitivity analysis conducted during the evaluation showed that the ICER is sensitive to the relationship between Ashworth scores and utility and the PBAC noted that the results of this and the re-calculation of the sensitivity analyses suggested an uncertainty over the true ICER. There was also disagreement between the ESC and the Pre-PBAC Response over the estimates of the utility gain which led to uncertainty about the reliability of the base-case ICER. The PBAC noted the ICERs were very sensitive to changes in QALY gains; a QALY gain of 0.170 resulted in an ICER of between $15,000 and $45,000 per QALY whereas a QALY gain of 0.117 resulted in an ICER of between $45,000 and $75,000 per QALY.

Overall, the PBAC considered that although the Ashworth scale was a reasonable measure of spasticity extrapolation to the economic model was highly uncertain. The PBAC therefore rejected the submission because of uncertainty in extrapolation of response in terms of the Ashworth scale to a quality of life measure, and high and uncertain cost-effectiveness.

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