PUBLIC SUMMARY DOCUMENT
Product: Botulinum toxin type A purified neurotoxin complex, lyophilised powder for I.M. injection, 100 units, Botox®
Sponsor: Allergan Australia Pty Ltd
Date of PBAC Consideration: November 2005

1. Purpose of Application

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

2. Background

At the May 1994 meeting, the PBAC recommended the Section 100 listing of botulinum toxin type A for blepharospasm in patients 12 years and older with the drug being directly distributed to the treating doctor. At the December 1999 meeting, the PBAC recommended extension to 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. The PBAC at its March 2001 meeting recommended listing for the treatment of cervical dystonia (spasmodic torticollis) when other pharmacological treatments have failed or are inappropriate.

3. Registration Status

Botulinum toxin is Therapeutic Goods Administration (TGA) registered for the following indications:

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

4. Listing Requested and PBAC's View

Botulinum Toxin Program Section 100
For the treatment of focal spasticity in adults.

The PBAC considered that if listing were to be recommended, a narrower restriction may help to identify those patients likely to derive the most benefit from a reduction in spasticity,

5. Clinical Place for the Proposed Therapy

Spasticity is one of the most common motor disorders and can be the consequence of a variety of disorders of the central nervous system, including stroke, multiple sclerosis, spinal cord diseases and craniospinal trauma.

Botox injection therapy treats spasticity by allowing the muscle to relax. The effects of Botox 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

The submission nominated placebo (standard medical management) as the main comparator. The comparator was considered appropriate by the PBAC.

7. Clinical Trials

The submission presented **s**ix (published) head-to-head randomised comparative trials comparing botulinum toxin type-A (BTx-A) and placebo, as detailed below. The trials that have common outcome measures were included in meta-analyses.

Trials included in the submission

Trial/first author	Citation	Publication Citation
BTOX-130-8051/ Simpson DM/ O'Brien CF	A double-blind, vehicle-controlled study to evaluate dosing, safety and efficacy of intramuscular botulinum toxin type A (BOTOX®) for the treatment of upper limb spasticity in post-stroke subjects.	*Neurology* 1996; 46:1306-10. *Neurology* 1995; 45(Suppl 4):A329.
BTOX-133/134-8051/ Childers MK	Multicenter, double-blind, placebo-controlled, parallel, dose-response clinical trial of intramuscular BOTOX® (botulinum toxin type A) purified neuroprotein complex for the treatment of upper limb spasticity in post-stroke patients.	*Neurology* 1999; 52:A295. *Archives of Physical Medicine and Rehabilitation* 2004; 85:1063-9.
191622-008/ Brashear A/	A multicenter, double-blind, randomized, placebo-controlled, parallel study of the safety and efficacy of BOTOX® (botulinum toxin, type A) purified neurotoxin complex in the treatment of focal upper limb spasticity post-stroke.	*New England Journal of Medicine* 2002; 347:395-400 *Neurology* 2001; 56:8(Suppl 3):A78.
BTOX-418/422-8051/ De Beyl	A multicenter, double-blind, vehicle-controlled, parallel study to evaluate dosing, safety and efficacy of intramuscular botulinum toxin type A (BOTOX®) for the treatment of upper limb spasticity in post-stroke subjects.	*European Journal of Neurology* 2000; 7(Suppl 3):23.
BTOX-702-8051/ Dunne J	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).	*Internal Medicine Journal* 2003; 33:A41.
Verplancke	A randomized controlled trial of botulinum toxin on lower limb spasticity following acute acquired severe brain injury.	*Clinical Rehabilitation* 2005; 19:117-25.

8. Results of Trials

The submission conducted a *post hoc* Ashworth Scale responder analysis (a responder was defined as a patient with a reduction of ≥2 points in the tonicity of any muscle. The submission claimed that a 2-point reduction in the Ashworth scale for any muscle represents a clinically important and patient relevant improvement; and facilitates the use of physical methods (eg. muscle lengthening or casting) in strengthening the muscle and rehabilitating the patient, helping to restore them to a level in which they can perform various activities of daily living.

The results of the meta-analyses showed there were significant differences between treatments in change from baseline in wrist and elbow flexor muscle tone, favouring botulinum toxin type-A. There was no difference between treatments (standard medical treatment and botulinum toxin type-A) in change from baseline in ankle plantar muscle tone

at Week 4, the primary endpoint of the trial, nor at Week 8 (the submission's preferred endpoint).

Various functional/disability scales were also used in the key trials, which the PBAC considered have greater overall patient relevance.

Functional Independence Measure – Composite score of physical functioning
The upper limb trials (130-8051, 133/134-8051 and 418/422-8051) measured changes in the Functional Independence Measure. There were no significant differences between treatments in any of the individual trials, nor in the meta-analysis of trials, at week 6 and trial endpoint.

Barthel Index
The lower limb Trial 702-8051 used the Barthel Index, which assesses the ability of patients to perform 10 tasks of everyday living on a score out of 20. There were no significant differences between treatments at 4, 8 or 16 weeks.

Disability Assessment Scale
Trial 191622-008 measured mean change in functional ability using the Disability Assessment Scale. In the trial, the investigator and patient selected (at baseline) one of the items (hygiene, dressing, pain or cosmesis) as the principal therapeutic target. The mean change in disability in the principal target and proportion of patients with a change ≥1 in their principal therapeutical target indicate there were significant differences between patients, favouring botulinum toxin type-A.

There were no differences between botulinum toxin type-A and placebo in the number of patients with any adverse event, serious adverse events, or in any individual adverse events.

For PBAC's view on trial results, see Recommendation and Reasons.

9. Clinical Claim

The submission claimed that botulinum toxin type-A has significant advantages in effectiveness over placebo and has similar toxicity.

The PBAC noted this claim was made on the basis of changes in the Ashworth Scale. Also, the PBAC noted the statistically significant differences between botulinum toxin and placebo in the Ashworth Scale do not translate to detectable differences in subjective functional assessments. Therefore, the PBAC did not accept the clinical claim.

10. Economic Analysis

The preliminary economic evaluation presented a cost-effectiveness approach. The PBAC considered this an appropriate approach. The resources included were drug costs, the costs of drug administration and monitoring costs.

The trial-based incremental cost per extra patient achieving ≥2-point reduction in the Ashworth (or expanded Ashworth) Scale at 6 weeks was $1,000-5,000 (and using 95% confidence limits of response: $1,000-5,000, $5,000-10,000).

A modelled economic evaluation with a time horizon of 6 months was presented. The resources included were drug costs, the costs associated with drug monitoring and

administration and the costs of physiotherapy and splinting/casting. The comparative costs and outcomes for each alternative and the incremental costs and outcomes are summarised below.

The base case modelled incremental cost per extra patient achieving ≥2-point reduction in the Ashworth (or expanded Ashworth) Scale over 6 months was more than the trial-based cost but less than $5,000.

The PBAC noted a cost-effectiveness approach based on the Ashworth Scale responder analysis is only valid if this outcome had been considered clinically important and patient relevant.

See also the Recommendation and Reasons for the PBAC's views.

11. Estimated PBS Usage and Financial Implications

The submission estimated the number of patients to commence Botox in Year 1 of listing to be less than 2,000 with a total of up to 2,000-10,000 patients in Year 4 of listing.

The cost to the PBS was estimated to up to $10,000-25,000 million in Year 4 of listing.

12. Recommendation and Reasons

The PBAC accepted expert advice that the Ashworth Scale, a measurement of muscle tone in any muscle, is a generally accepted measure of spasticity response and that a reduction of 2 points is a significant change in spasticity. However, there are doubts about the clinical importance and patient relevance of the submission's post hoc Ashworth Scale responder analysis. This is because the statistically significant differences between botulinum toxin (BTx-A) and placebo in the Ashworth Scale do not translate to detectable differences in subjective functional assessments. Although these are secondary outcomes in the trials, the PBAC agreed they have greater overall patient relevance. It was unclear whether the Disability Assessment Scale reporting statistically significant differences between BTx-A and placebo reported in Trial 191622-008 adequately measured functional change in patients because each patient must choose only one of the following attributes for assessment during the trial: hygiene, dressing, pain or cosmesis. From a clinical perspective, reducing spasticity with BTx-A in a paretic limb may be of little benefit to a stroke patient (post-stroke spasticity accounted for the majority of trial patients and is likely to be a common reason to consider trying BTx-A). BTx-A would potentially benefit patients functionally if release of spasticity in the fingers or wrist restores traction. The PBAC noted that no other data on the functional benefits or implications of response to BTx-A treatment were presented to help interpret these results.

The PBAC also noted that assessment of treatment under the Functional Independence Measure and the Barthel Index showed no significant differences between treatments.

The main issue of economic uncertainty was that the claimed physiotherapy cost off-sets are not clinically supported because the majority of the patients who are post-stroke patients will continue to need physiotherapy. The PBAC considered that the assumed difference in extent of physiotherapy support between "responders" and "non-responders" was not adequately justified. The PBAC further noted expert advice presented at the sponsor's hearing that response to BTx-A provided a window of opportunity for physical therapies to help regain

muscle or joint function and that use of BTx-A in clinical practice was usually limited to 1-3 doses. This might suggest that BTx-A-treated patients would require more physiotherapy rather than less, as assumed for the 6-month duration of the model.

Therefore, the PBAC considered that if listing were to be recommended, a narrower restriction may help to identify those patients likely to derive the most benefit from a reduction in spasticity, for example by being able to undergo physiotherapy to achieve a longer-term response, by identifying patients manifesting more severe spasticity at baseline, and by identifying particular types of potentially reversible focal spasticity associated with the most functional impairment. Further, that a limitation on the number of treatment doses was appropriate as no justification had been provided for longer periods of therapy.

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.

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