PUBLIC SUMMARY DOCUMENT
Product: Botulinum toxin type A purified neurotoxin complex, lyophilised powder for IM injection, 100 units vial, Botox®
Sponsor: Allergan Australia Pty Ltd
Date of PBAC Consideration: July 2008

1. Purpose of Application

The submission sought to extend the current section 100 listing (Botulinum Toxin Program) 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.

2. Background

At the November 2005 PBAC meeting, the PBAC rejected an application to extend the Section 100 listing for botulinum toxin type A (Botox) 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 PBAC Public Summary Document – November 2005)*

At the July 2006 PBAC meeting, the PBAC again rejected a submission seeking for the treatment of focal spasticity (upper and lower limbs) in adult patients who meet certain criteria 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. *(See PBAC Public Summary Document – July 2006)*

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)

Treatment of moderate to severe spasticity of the lower limb in ambulatory adults following a stroke as second line therapy when standard management has failed or as an adjunct to physical therapy.

To qualify for therapy patients must:

1. be ambulatory, with or without assistive devices/support
2. have no fixed muscle contracture in the targeted muscles for injection that would limit treatment efficacy
3. have spasticity which reduces walking speed

4. have a walking speed < 48 m/min over 10 metres, based on the standard 10 metre walk speed assessment.

To continue treatment after the first year:
Based on the standard 10 metre walk test, all patients must improve their walk distance by at least 15 m/min, relative to their baseline speed, in order to obtain continuing treatment.

For PBAC's view, see Recommendation and Reasons.

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

The submission nominated placebo as the main comparator, which was previously accepted by the PBAC at the July 2006 meeting.

7. Clinical Trials

The submission provided new efficacy data from trial 702-8051. The gait speed was measured and patients were allocated to one of four functional walking categories. The change in categories after treatment was analysed.

Only one supplementary randomised trial, which was presented in the previous submission, was published at the time of the submission, as follows:

Trial/First author	Protocol title	Publication citation
Supplementary randomised trials		
Verplancke et al (2005)	A randomised controlled trial of Botulinum toxin on lower limb spasticity following acute acquired severe brain injury	Clinical Rehabilitation (2005). 19(2):117-25

8. Results of Trials

In terms of the distribution of patients into functional walking categories in trial 702-8051, the submission reported that there was no difference between the BTx-A and placebo treatment groups at baseline, but after treatment there was a statistically significant difference between the groups. The submission claimed that a larger proportion of patients moved to a higher functional walking category in the BTx-A treatment group compared to the placebo group.

The claim of superior efficacy was based on a difference in the distribution in walking categories between the groups post treatment only. The submission did not present the results in terms of change from baseline.

For PBAC's comments on these results, see Recommendation and Reasons.

The submission presented new toxicity data: a) meta-analysis of discontinuation rates and adverse events in ten RCTs for the treatment of focal spasticity (upper or lower limb); b) data from post marketing surveillance.

The submission reported no significant differences in the incidence of adverse events between the two treatments. However, there are recent concerns regarding the safety profile of BTx-A from various drug regulatory agencies: FDA, Health Canada and Medicines and Healthcare products Regulatory Agency (MHRA) due to distant spread of BTx-A from the site of injection.

9. Clinical Claim

The submission claimed that BTx-A was therapeutically superior and equivalent in terms of comparative safety to placebo.

The PBAC did not accept this claim, *see Recommendation and Reasons.*

10. Economic Analysis

The submission presented an updated modelled economic evaluation (cost-utility). The utility values were obtained using the assessment of quality of life (AQoL) questionnaire in 127 BTx-A patients, using similar selection criteria employed in the key trial. Patients in the trial and the utility studies were grouped into one of the four functional walking categories based on gait speed and each category was assigned a utility value. The incremental cost effectiveness ratio (ICER) was estimated to be in the range of $15,000- 45,000 per quality adjusted life year (QALY).

Additional analyses were conducted during the evaluation. The model was sensitive to the utility values based on cause of the spasticity, number of walking speed categories and the number of vials per course of BTx-A treatment.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated to be less than 10,000 in Year 5.

The financial cost per year to the PBS was estimated to be in the range of $10 – 30 million in Year 5.

12. Recommendation and Reasons

The PBAC noted that the requested listing was for lower limb spasticity post stroke but that the evidence provided only included patients suffering from post stroke equinovarus deformity and the assumption that the results are applicable to the broader population was not reasonable. The PBAC however noted that the sponsor would accept the narrower listing of post stroke equinovarus deformity if a positive recommendation was received.

The PBAC considered that there was considerable uncertainty in the clinical outcomes from the pivotal trial, 7028051. The efficacy results from this study provided in this submission were from a post-hoc analysis. The assignment of patients into walking categories was based purely on gait speed, and the relevance of the walking categories in determining change in overall patient functionality remains uncertain. Additionally, the placebo group had greater

disability at baseline which favoured botulinum. The claim of superior efficacy is based on a difference in the distribution in walking categories between the groups post treatment only. The results of an analysis of change from baseline conducted during the evaluation suggest that there is no difference between the treatment groups in terms of change from baseline mobility (as defined by functional walking group) or responder rate (where a responder is defined as any patient who improves by at least one functional walking category from baseline). It is, however, acknowledged that the representativeness of these results is limited by the small size of the trial population.

Two supplementary studies, 138/139-8051 and 191622-501/502, also failed to show significant improvements in functionality. The PBAC further noted that duration of any response to botulinum toxin may be short (4-8 weeks) and that this may have implications if continuing treatment is limited to one per year.

Overall, the PBAC considered that the data provided failed to show either evidence for a sustained benefit with botulinum treatment, or evidence that a short term improvement allows a window in which, for example, additional physiotherapy may be undertaken to give longer term benefit.

The PBAC noted the participants in the utility study were different (healthier) than the patients in the trial, which may have resulted in the utility values being systematically overestimated. Additionally, the utility values were estimated in the absence of treatment with botulinum and therefore did not take into account any treatment related side-effects. The PBAC further noted that when the base case was reset to account for errors in the original analysis (utility adjusted for injection schedule, discounted utilities, and inclusion of physical therapy costs) the incremental cost/QALY was between $75,000 - $105,000, an increase of between $45,000 - $75,000 on the base case presented in the submission. The Committee considered that there was considerable residual uncertainty in this estimate due to significant overestimation of the benefit and underestimate of total cost.

Therefore, the PBAC rejected the submission because of uncertain clinical benefit and the resulting high and uncertain cost-effectiveness.

Recommendation
Reject

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 is disappointed with the PBAC's decision but acknowledges the limitations in the trial evidence. It will examine whether additional clinical evidence can be made available to support a re-submission.