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 2009

1. Purpose of Application

The submission sought to extend the current Section 100 (Botulinum Toxin Program) listing for botulinum toxin type A to include the treatment of severe hyperhidrosis of the axillae in adolescents and adults following failure of topical treatments to reduce sweating.

2. Background

Botulinum toxin type A had not been previously considered by the PBAC for the treatment of severe hyperhidrosis of the axillae.

3. Registration Status

Botulinum toxin type A for the treatment of severe primary hyperhidrosis of the axillae was TGA registered on 17 January 2002.

Botulinum toxin type A is also TGA registered for the following:

- Blepharospasm associated with dystonia, including benign blepharospasm and VII nerve disorders (specifically hemifacial spasm) in patients twelve years and over;
- Cervical dystonia (spasmodic torticollis);
- Dynamic equinus foot deformity due to spasticity in juvenile cerebral palsy patients two years of age or older;
- Glabellar lines associated with corrugator and/or procerus muscle activity;
- Focal spasticity in adults;
- Spasmodic dysphonia;
- Strabismus in children and adults; and
- Focal spasticity of the upper and lower limbs, including dynamic equinas foot deformity, due to juvenile cerebral palsy in patients two years of age and older.

4. Listing Requested and PBAC's View

Option 1
Section 100 (Botulinum Toxin Program)
For the treatment of severe primary axillary hyperhidrosis in adult and adolescent patients (>12 years of age) that have been diagnosed with focal, visible, excessive sweating of the axillae of at least 6 months duration without apparent cause with at least two of the following characteristics:

- Bilateral and relatively symmetric
- Impairs daily activities
- Frequency of at least one episode per week
- Age of onset less than 25 years
- Positive family history
- Cessation of focal sweating during sleep

AND
Have failed or are intolerant to treatment with topical Aluminium chloride hexahydrate following a trial period of at least 1-2 months.

Maximum number of treatments per year is 2.

Option 2
Section 100 (Botulinum Toxin Program)
For the treatment of severe primary axillary hyperhidrosis in patients:

- Diagnosed with severe primary hyperhidrosis of the axillae for at least six months.
- That have failed or are intolerant to treatment with topical Aluminium chloride hexahydrate following a trial period of at least 1-2 months, and
- where the baseline gravimetric measure exceeds the following:
    - Adults (>18 years of age): Women: 100 mg of spontaneous resting axillary sweat production in each axilla measured gravimetrically at room temperature over a period of 5 minutes. Men: 150 mg of spontaneous resting axillary sweat production in each axilla measured gravimetrically at room temperature over a period of 5 minutes in men.
    - Adolescents (12-17 years of age): > 50 mg of spontaneous resting axillary sweat production in each axilla measured gravimetrically at room temperature over a period of 5 minutes.

Maximum number of treatments per year is 2.

The PBAC considered Option 1 to be the most appropriate and consistent with current clinical practice. The PBAC noted that Option 2 uses gravimetric assessment as an objective measure for diagnosis, but that it would be impractical for use in the clinical setting.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Hyperhidrosis is a condition characterised by excessive sweat production due to over-activity of the sweat glands of the palms, axillae, soles of the feet or face. Hyperhidrosis can be classified as either focal or generalised, and either primary or secondary.

Current treatment options include non PBS-subsidised medical treatments such as topical aluminium chloride salts, anticholinergic drugs and inotophoresis or surgery.

Botulinum toxin type A would provide an alternative PBS-subsidised treatment for the treatment of severe primary axillary hyperhidrosis.

6. Comparator

The submission nominated placebo, administered by intradermal injection, as the main comparator.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The submission presented three randomised trials comparing botulinum toxin type A with placebo in patients with severe primary axillary hyperhidrosis (trial 191622-505, 191622-016 and Connor 2006). Three open-label studies were also presented as supportive evidence

(study 191622-506, 191622-513 and 191622-075). Details of the trials published at the time of the submission are in the table below.

Trial ID / First author	Protocol title / Publication title	Publication citation
Direct randomised trials		
Trial 191622-016		
Kowalski JW et al (2004)	Quality-of-life effect of botulinum toxin type A on patients with primary axillary hyperhidrosis: results from a North American clinical study population.	*Journal of the American Academy of Dermatology* 2004, 50(3): P50 Abstract P196
Lowe NJ et al (2004)	Botulinum toxin type A in primary axillary hyperhidrosis: a 52-week, multicentre, double-blind, randomised, placebo-controlled trial.	*Journal of the American Academy of Dermatology* 2004, 50(3): P50 Abstract P195
Trial 191622-505		
Lowe NJ et al (2002)	Effect of botulinum toxin type A on quality of life measures in patients with excessive axillary sweating: A randomised controlled trial.	*Journal of Investigative Dermatology* 2002, 119(1): 241. Abstract 202
Naumann M et al (2001)	Botulinum toxin type A in treatment of bilateral primary axillary hyperhidrosis: randomised, parallel group, double-blind, placebo-controlled trial.	*BMJ* 2001, 323: 596-599
Naumann MK et al (2002)	Effect of botulinum toxin type A on quality of life measures in patients with excessive axillary sweating: a randomised controlled trial.	*British Journal of Dermatology* 2002, 147(6): 1218-1226
Connor 2006		
Connor KM et al (2006)	Botulinum toxin treatment of social anxiety disorder with hyperhidrosis: a placebo-controlled double-blind trial.	*Journal of Clinical Psychiatry* 2006, 67(1): 30-36
Connor KM et al (2004)	Botulinum toxin treatment of social anxiety disorder with hyperhidrosis: a double-blind, placebo-controlled trial.	*Neuropsychopharmacology* 2004, 29(S1): S96 Abstract 81
Supplementary studies		
Study 191622-509		
Lowe PL et al (2003)	Botulinum toxin type A in the treatment of bilateral primary axillary hyperhidrosis: efficacy and duration with repeated treatments.	*Dermatologic Surgery* 2003, 29(5): 545-548
Naumann M et al (2003)	Botulinum toxin type A is a safe and effective treatment for axillary hyperhidrosis over 16 months: a prospective study.	*Archives of Dermatology* 2003, 139(6): 731-736

8. Results of Trials

The primary outcomes in the direct randomised trials were based on either gravimetric assessment or Hyperhidrosis Disease Severity Scale (HDSS) response. The HDSS is a self-reported scale where patients are asked to rate their condition on a 4-point scale of: 1= never noticeable/never interferes with daily activities; 2= tolerable/sometimes interferes; 3= barely tolerable/frequently interferes; 4= intolerable/always interferes. For gravimetric assessment, a 50% responder was a patient who achieved at least a 50% reduction from baseline in axillary sweat production. For the HDSS, a responder was defined as a patient who reported at least a two-grade improvement on the 4-point scale.

Gravimetric responder analysis was the primary outcome in trial 191622-505, and a secondary outcome in trial 191622-016. Statistically significant differences between treatment groups in favour of botulinum toxin type A were observed at all stages of evaluation for both trials. The meta-analysis presented used the gravimetric responder analysis results at week 4 in trial 191622-505 and week 4, session 1 in trial 191622-016. The results of the meta-analysis demonstrated that botulinum toxin type A was statistically significantly superior to placebo at reducing baseline axillary sweating by at least 50% at 4 weeks post-first treatment.

Proportion of patients obtaining a 2-grade improvement on the HDSS

	Bot n/N (%)	Placebo n/N (%)	RR (95% CI)	RD (95% CI)
191622-016[a]	57/104 (54.8)	6/108 (5.6)	**9.87 (4.45, 21.89)**	**0.49 (0.39, 0.60)**
Connor 2006[a,b]	15/20 (75.0)	3/20 (15.0)	**5.00 (1.71, 14.63)**	**0.60 (0.35, 0.85)**

Abbreviations: Bot: botulinum toxin type A; RR: relative risk; RD: risk difference; CI: confidence interval

[a] Primary outcome in this trial

[b] Trial recruited patients diagnosed with social anxiety disorder

For the outcome of proportion of patients obtaining a 2-grade improvement on the HDSS, the PBAC noted that the results were clinically and statistically significant in favour of botulinum toxin type A over placebo.

The PBAC noted that in the direct randomised trials, statistically significantly more treatment-related adverse events were reported in the botulinum toxin type A treatment arms compared to the placebo arm. In trial 191622-505, statistically significantly more placebo patients reported an infection, predominantly described as a "common cold". No individual adverse events were reported statistically significantly more often in the botulinum toxin type A treatment arm than the placebo arm. In trial 191622-016, more overall events, flu syndrome, pharyngitis and non-axillary sweating (compensatory) events were reported in the botulinum toxin type A arm than the placebo arm. These differences were statistically significant.

9. Clinical Claim

The submission described botulinum toxin type A as superior in terms of comparative effectiveness and equivalent or inferior in terms of comparative safety over placebo for the treatment of primary axillary hyperhidrosis.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a trial-based economic evaluation, providing an estimate of the incremental cost per additional responder following a single botulinum toxin type A injection, based on the direct randomised trials (4-week duration) and a cost-utility economic evaluation (one year duration). The cost-utility economic evaluation presented a cost per quality adjusted life year (QALY), using trial derived utilities that had been extrapolated to 12 months.

The cost-utility economic evaluation provided an estimated incremental cost per QALY of between $15,000 and $45,000 for patients receiving 1.46 treatments per year.

A number of sensitivity analyses were conducted during the evaluation to reflect higher potential costs and reduced effects of botulinum toxin type A under the requested restriction. The cost per QALY was increased (but within the same range) when a scenario assuming a higher number of treatments per year and a lower utility change from baseline was used.

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 between 10,000 and 50,000 in Year 5 with a financial cost per year to the PBS estimated to be less than $10 million in Year 5.

The PBAC considered these estimates to be uncertain.

12. Recommendation and Reasons

The PBAC noted that no other second line treatments for severe hyperhidrosis of the axillae were available on the PBS, and that currently the only option for patients following failure of aluminium based anti-perspirants was surgery. The PBAC agreed that the appropriate comparator was placebo, as surgical options are rarely used. The PBAC also agreed that there was significant impact on the quality of life of the patients with hyperhidrosis and that there was a clinical need for botulinum toxin.

Of the two requested listing options, the PBAC considered Option 1 to be the most appropriate and consistent with current clinical practice. The PBAC noted that Option 2 uses gravimetric assessment as an objective measure for diagnosis, but it would be impractical for use in the clinical setting.

The submission presented three direct randomised trials (191622-505, 191622-016 and Connor 2006) comparing botulinum toxin type A with placebo in patients with severe primary axillary hyperhidrosis. Three open-label studies (study 191622-506, 191622-516 and 191622-075) were also presented as supportive evidence. The PBAC noted that while all trials used the TGA-approved dose of 50 U into each axilla, there was variation with regard to frequency of re-treatment between the trials. None of the trials assessed the dosing frequency requested in the restriction of a maximum of two treatments per year.

The primary outcomes in the direct randomised trials were based on either gravimetric assessment or Hyperhidrosis Disease Severity Scale (HDSS) response. The PBAC accepted the submission's claim of superiority in terms of comparative effectiveness and equivalent or inferior in terms of comparative safety over placebo for treatment of primary axillary hyperhidrosis, noting that the results were clinically and statistically significant in favour of botulinum toxin type A over placebo for all primary outcomes in the direct randomised trials and that statistically significantly more treatment-related adverse events were reported in the botulinum toxin type A treatment arms compared to the placebo arms.

The PBAC noted that the average number of treatments per year used in the economic evaluation were estimated to be 1.46 from trials 016 and 505/506, or 1.36 from trial 505/506 only. These trials allowed treatment every 8 weeks. However, the requested listing limited the number of treatment per year to two and sensitivity analyses assuming two treatments per year were conducted during the evaluation. The PBAC agreed with the sponsor's Pre-Sub-

Committee Response that to better reflect the trial approach up to 3 treatments per year may be more appropriate in the PBS restriction, and this is consistent with the dosage in the Product Information of repeat injections at intervals of no less than four months. The average number of treatments per year in the adolescent study 075 (1.90) was excluded from the economic evaluation and was considered reasonable as the proportion of adolescents in the subsidy pool was likely to be low.

The PBAC also considered that uncertainty existed with the application of utility values for one year in the economic model. The PBAC agreed that there was uncertainty in assigning constant improved utility to patients for the entire year, with the exception of allowing one week for onset of effect. It was considered that there may be some loss of effect leading up to requirement for subsequent treatment, which was not considered in the model, and that it may not be reasonable to assume there is a constant relationship between gravimetric response and utility as was applied by this assumption.

The cost-utility economic evaluation provided an estimated incremental cost per QALY of between $15,000 and $45,000 for patients receiving 1.46 treatments per year. The PBAC noted that the results of the sensitivity analysis conducted during the evaluation indicated that the model was quite sensitive to both the number of treatments per year, and the value used for the difference in utility change from baseline between the treatment groups. The cost per QALY increased (within the same range) when a scenario considered by the PBAC to be more representative of the likely Australian situation was used (three treatments per year and lower utility change from baseline). Therefore, the PBAC considered that the ICER is likely to be greater than the estimated base-case if the uncertainty around the utility value and the duration of response through the entire period between treatments is taken into account. This was considered to be high in the context of the condition.

The PBAC therefore rejected the submission on the basis of high and uncertain cost-effectiveness.

The PBAC noted that the submission met the criteria for an Independent Review.

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

Allergan Australia welcomes the PBAC's acknowledgement of the clinical need for BOTOX® for hyperhidrosis and the significant impact of the condition on patients' quality of life. Allergan will continue to work with the PBAC to make BOTOX® available under the PBS for the treatment of hyperhidrosis.