

## **PUBLIC SUMMARY DOCUMENT**

**Product:** BOTULINUM TOXIN TYPE A PURIFIED NEUROTOXIN COMPLEX, lyophilised powder for IM injection, 100 units, Botox<sup>®</sup>

**Sponsor:** Allergan Australia Pty Ltd.

**Date of PBAC Consideration:** March 2010

### **1. Purpose of Application**

The resubmission sought an extension to the current Section 100 (Botulinum Toxin Program) listing for botulinum toxin type A to include treatment of severe hyperhidrosis of the axillae in adolescent and adult patients following failure of topical treatments.

### **2. Background**

At the November 2009 meeting, the PBAC rejected a submission to list botulinum toxin type A for the treatment of severe hyperhidrosis of the axillae on the basis of high and uncertain cost-effectiveness. 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.

The PBAC considered that uncertainty existed with the application of utility values for one year in the economic model, with the exception of allowing one week for onset of effect. The PBAC noted that the results of the sensitivity analysis conducted during the evaluation indicated that the model was 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.

For further details see the botulinum toxin Public Summary Document (PSD) for the November 2009 PBAC meeting at:

[www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-Botulinum-nov09](http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-Botulinum-nov09)

### **3. Registration Status**

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

### **4. Listing Requested and PBAC's View**

#### 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:

- 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 3 (repeat injections at intervals of no less than 4 months).

The PBAC considered that the restriction wording requested in the submission, as amended in the Restrictions Working Group advice, was appropriate, noting that compared to the previous submission the new restriction increases the maximum number of treatments per year from 2 to 3 and relies upon a diagnosis of severe primary axillary hyperhidrosis without including the characteristics of this condition.

## **5. Clinical Place for the Proposed Therapy**

Hyperhidrosis is a condition characterised by excessive sweat production. Hyperhidrosis can be classified as either focal or generalised, and either primary or secondary. The most common form of focal hyperhidrosis is primary focal hyperhidrosis, resulting from over-activity of the sweat glands of the palms, axillae, soles of the feet or face. Focal hyperhidrosis may also occasionally arise secondary to spinal cord injury, some polyneuropathies or internal diseases.

Current treatment options include non PBS-subsidised medical treatments such as topical aluminium chloride salts, anticholinergic drugs and iontophoresis or surgery. Botulinum toxin type A would provide an alternative PBS-subsidised treatment for the severe primary axillary hyperhidrosis.

## **6. Comparator**

The November 2009 submission nominated placebo as the main comparator. This was considered appropriate by the PBAC.

## **7. Clinical Trials**

No new trial data were presented in the re-submission. The re-submission:

- aimed to address the areas of uncertainty highlighted by the PBAC with respect to the economic model and the resulting incremental cost-effectiveness ratios (ICERs), specifically the frequency of treatment, the number of treatments per year, and the utility values;
- provided ICER estimates incorporating a price reduction.

For details of trials published at the time of the submission refer to the Public Summary Document for the November 2009 meeting.

## **8. Results of Trials**

### Frequency of treatment

The re-submission requested a maximum number of treatments per year of 3, as previously agreed by the PBAC to be more appropriate and consistent with the approved product information. The submission stated that this represented the maximum number of doses available under the PBS, however, in practice, it was likely that the average number of treatments per patient per year would be consistent with those used in the economic evaluation (1.46 or 1.36). The submission asserted that it was unlikely that the restriction allowing up to 3 doses per year would result in an increase in the average number of doses than that found in the clinical trials.

### Number of treatments per year

The submission presented the results of studies 016, 505/506 and 513, used to determine the average number of treatments per year in the economic evaluation. Study 016 was a 52-week, multicentre, double-blind, randomised, placebo-controlled, parallel group study.

Patients were able to request re-treatment up to every 8 weeks (up to week 44) providing they reported an HDSS score of 3 or 4 and produced at least 50 mg spontaneous resting axillary sweat in each axilla over 5 minutes. Patients treated with 100 U botulinum toxin received a mean of 1.5 treatments during the 52-week trial.

Study 506 was an open-label study to assess the safety of repeated treatments with botulinum toxin type A in subjects with primary hyperhidrosis that had completed trial 505 (a 16-week placebo-controlled study). Patients in this trial were able to request re-treatment at any time up to week 32 and were eligible for re-treatment every 16 weeks if their gravimetric assessment indicated sweat production in both axillae of at least 50 % of their baseline assessment in study 505. This allowed for a maximum of three treatments. Study 506 was of 52 weeks duration, providing a total of 68 weeks of observation. The submission stated that for patients receiving botulinum toxin in study 505, only 1.8 doses were received in the 68 week period covered by the studies which equated to a mean of 1.4 doses per year.

Study 513 enrolled patients with lower baseline gravimetric levels and did not include an inclusion criterion of at least 50 mg per 5 minutes of sweat production. This was a population with milder disease severity to that for whom listing was sought. The average number of treatments in study 513 was 1.32, which the submission claimed was consistent with the two other studies.

The submission stated that advice received from clinicians treating hyperhidrosis in Australia indicated that dosing frequency would be consistent with the trial based results (with a frequency of not more often than one treatment every 8 months for the average patient). Consistent with the November 2009 submission, the re-submission used 1.36 and 1.46 treatments per patient per year in its revised economic evaluation.

#### Utility values

In response to PBAC's concern 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, the submission stated that this was a difficult issue to resolve, given that data to model an alternative scenario precisely did not currently exist.

*For PBAC's views, see Recommendation and Reasons*

### **9. Clinical Claim**

This was a minor submission to PBAC. The clinical claim for the November 2009 major 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.

### **10. Economic Analysis**

The revised incremental cost-effectiveness ratio (ICER) was in the range of \$15,000 - \$45,000 per quality adjusted life-year (QALY) gained.

*For PBAC's views, see Recommendation and Reasons*

### **11. Estimated PBS Usage and Financial Implications**

The resubmission estimated the likely number of patients per year to be in the range of 10,000 – 50,000 in Year 5, while the financial cost per year to the PBS was estimated to be less than \$10 million in Year 5.

## **12. Recommendation and Reasons**

The PBAC recommended the availability of botulinum toxin type A purified neurotoxin complex (Botox) under the PBS Section 100 Botulinum Toxin Program be extended to include treatment of severe primary axillary hyperhidrosis on a cost-effectiveness basis over placebo at the new price proposed.

In making this recommendation, the Committee recalled that it had rejected a submission seeking to subsidise Botox for this use at its November 2009 meeting on the basis of high and uncertain cost-effectiveness. The current submission's offer of a price reduction for the hyperhidrosis indication reduced this ICER further within the \$15,000 - \$45,000 range, which the Committee considered represented acceptable cost-effectiveness in the context of this disease.

The PBAC considered that the restriction wording requested in the submission, as amended in the Restrictions Working Group advice, was appropriate, noting that compared to the previous submission the new restriction increases the maximum number of treatments per year from 2 to 3 and relies upon a diagnosis of severe primary axillary hyperhidrosis without including the characteristics of this condition. The PBAC further agreed that dermatologists be added to the list of authorised prescribers of botulinum toxin type A.

### ***Recommendation:***

BOTULINUM TOXIN TYPE A PURIFIED NEUROTOXIN COMPLEX, Lyophilised powder for injection 100 units

Remove the “*I.M.*” from the product description in the Schedule and add the following indication to the current restriction:

#### Section 100 listing (Botulinum Toxin Program)

Treatment of severe primary axillary hyperhidrosis in a patient 12 years or older who has failed or is intolerant to topical aluminium chloride hexahydrate after one to two months of treatment.

Maximum number of treatments per year is 3, with no less than 4 months to elapse between treatments.

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**

Allergan Australia welcomes the PBAC's recommendation that BOTOX<sup>®</sup> be made available to patients suffering from severe hyperhidrosis of the axillae.