PUBLIC SUMMARY DOCUMENT
Product: Botulinum Toxin Type A Purified Neurotoxin Complex, lyophilised powder for injection, 100 units, Botox®
Sponsor: Allergan Pty Ltd
Date of PBAC Consideration: July 2012

1. Purpose of Application

Resubmission to extend the current Section 100 (Botulinum Toxin Program) listing to include the prophylaxis of headaches in adult patients with chronic migraine who meet certain criteria.

2. Background

At the November 2011 meeting, the PBAC rejected a submission to list botulinum toxin type A for the prophylaxis of headaches in adult patients with chronic migraine who meet certain criteria on the basis of uncertain clinical benefit and high and highly uncertain cost effectiveness.

3. Registration Status

Botulinum toxin type A purified neurotoxin complex was TGA registered on 15 March 2011 for the indication:

Prophylaxis of headaches in adults with chronic migraine (headache on at least 15 days per month of which at least 8 days are with migraine).

Botulinum toxin type A purified neurotoxin complex is also TGA registered for the following indications:

- 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;
- Focal spasticity in adults;
- Strabismus in children and adults; and
- Focal spasticity of the upper and lower limbs, including dynamic equinus foot deformity, due to juvenile cerebral palsy in patients two years of age and older.
- severe primary hyperhidrosis of the axillae
- Spasmodic dysphonia

Botulinum toxin type A purified neurotoxin complex is indicated for the following cosmetic indications:

- Temporary improvement in the appearance of upper facial rhytides (glabellar lines, crow's feet and forehead lines) in adults

4. Listing Requested and PBAC's View

Section 100 Botulinum Toxin Program
Authority Required
Prophylaxis of headaches in an adult patient with chronic migraine who fulfil the following criteria:

1. Patient has experienced an average of 15 or more headache days per month, with at least 8 days of migraine, over a period of at least 6 months
2. Inadequate response, intolerance or contraindication to at least three migraine prophylactic medications.

Treatment should be discontinued if the patient does not respond after two treatments. Treatment response is defined as:
[CONTINUATION RULE WORDING OPTION 1]: A 50% or greater reduction from baseline in the number of headache days per month by week 24.

[CONTINUATION RULE WORDING OPTION 2]: A 50% or greater reduction from baseline in the number of headache days per month, or a 30% or greater reduction from baseline in the number of moderate to severe headache days per month, by week 24.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Migraine is a primary headache disorder that manifests as severe headache, typically with an intense throbbing pain that is aggravated by routine physical activity. Patients may also have associated symptoms such as nausea, vomiting, visual problems and increased sensitivity to light or sound.

Chronic migraine (CM) is a sub-type of chronic daily headache (CDH) and is defined as headache on at least 15 days per month, with at least 8 headache days meeting the criteria for migraine without aura. In contrast, patients with episodic migraine (commonly referred to as 'migraine') have headache on less than 15 days per month. CDH including CM is associated with significantly greater impairment in quality of life (QoL) compared with episodic headache. Patients with CM also have higher rates of co-morbid conditions including anxiety, depression, obesity and cardiovascular diseases or risk factors compared to those with episodic migraine.

Drug therapy options for patients with frequent headaches include acute pain medications and preventive treatments (prophylaxis). The aims of prophylaxis are to reduce attack frequency, severity and duration; reduce the risk of medication overuse, defined as 10-15 days or more per month of certain analgesics; and improve QoL.

The submission proposed that the place in therapy of botulinum toxin type A for refractory chronic migraine is as last line treatment after the patient has failed to achieve an adequate response to at least three migraine oral prophylactic medications, or is intolerant to or in whom the available migraine prophylactic medications are contraindicated.

6. Comparator

The re-submission nominated best supportive care (BSC) as the comparator, on the basis that changing the restriction to patients who have failed three or more prior prophylactic medications positions botulinum toxin A (hereafter named Botox) as last line treatment.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The scientific basis of the re-submission was unchanged from the previous submission. Additional post-hoc subgroup analyses using data from the PREEMPT I and II trials were presented for the 'three or more prior prophylactics' subgroup.

The table below details the published trials and associated reports presented in the re-submission:

Trial ID / First author	Protocol title / Publication title	Publication citation
PREEMPT I (191622-079)	A multicenter study evaluating the efficacy and safety of BOTOX purified neurotoxin complex as headache prophylaxis in migraine patients with 15 or more headache days per 4 week period a 24 week, double-blind, randomised, placebo-controlled, parallel-group phase followed by a 32-week open-label extension phase.	
Aurora SK et al 2010	OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT I trial.	Cephalalgia 30 (7): 793-803
PREEMPT II (191622-080)	A multicenter study evaluating the efficacy and safety of BOTOX® (Botulinum Toxin Type A) purified neurotoxin complex as headache prophylaxis in migraine patients with 15 or more headache days per 4-week period in a 24-week, double-blind, randomised, placebo-controlled, parallel-group phase followed by a 32-week open-label extension phase.	
Diener HC at al 2010	OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT II trial.	Cephalalgia 30 (7): 804-14
Pooled-analyses of direct randomised trials		
PREEMPT (pooled analysis)	Clinical Overview from TGA Submission.	Allergan. 2009
Dodick DW at al 2010	OnabotulinumtoxinA for treatment of chronic migraine: Pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program.	Headache 50 (6): 921-36
Blumenfeld A et al 2010	Method of injection of OnabotulinumtoxinA for chronic migraine: a safe, well-tolerated, and effective treatment paradigm based on the PREEMPT clinical program	Headache 50: 1406-18.

8. Results of Trials

The results for the ITT population (presented previously) and the subgroup using ≥3 prior prophylactic medications (new in the re-submission) for PREEMPT pooled data of change in headache days from baseline at week 24 are presented below.

Comparison between ITT and ≥3 prior prophylactic subgroup for change in headache days per 28 day period in PREEMPT pooled data

	Botox Mean (SD)			BSC Mean (SD)			Difference Mean (95% CI)
Population	**N**	**Baseline**	**Change**	**N**	**Baseline**	**Change**	**Change**
ITT	688	19.9 (3.7)	−8.4 (6.6)	696	19.8 (3.7)	−6.6 (6.7)	**−1.8 (−2.52, −1.13) P<0.05**
≥3 prior prophylactics	231	20.0 (3.5)	−7.4 (6.6)	248	20.2 (3.9)	−4.7 (6.4)	**−2.6[a] -2.7 (−3.81, −1.48) P<0.05**

ITT = intention to treat; SD = standard deviation; BSC = best supportive care; CI = confidence interval
[a] The mean difference (95%CI) values reported in two sections of the submission differ. The difference should be -2.7.

The pooled analysis of the PREEMPT data demonstrated a statistically significant difference between botulinum toxin and BSC for change in headache days in both the intention to treat (ITT) population (mean difference -1.8; 95% CI: -2.52, -1.13) and the 'three or more prior prophylactics' subgroup (mean difference -2.7; 95% CI: -3.81, -1.48).

The re-submission presented additional quality of life results, not presented in the previous submission, from the Headache Impact Test (HIT-6) and Migraine Specific Quality of Life (MSQ) questionnaires for patients in the ITT and ≥3 prior prophylactics subgroup. The results suggest a clinically meaningful improvement for Botox compared to BSC treatment.

The mean difference in the HIT-6 score was -2.4 (95% CI: -3.11, -1.72) for the ITT population and -2.1 (-3.18, -0.99) for the subgroup of ≥3 prior prophylactics, which for the ITT population, but not the subgroup of interest, slightly exceeded the minimum clinically important difference (MCID) between groups of -2.3.

The MCID for changes within groups (individual level) have been established as: Role Restrictive (RR) =+10.9, Role Preventative (RP) =+8.3, Emotional Function (EF) =+12.2 (Dodrick et al, 2007). Based on this definition, there was a statistically significant improvement in all three MSQ domains for both ITT (RR==-17.0, RP=-13.1, EF=-17.9) and >=3 prior prophylactics subgroup (RR=-14.0, RP=-10.7, EF=-15.9)

As it is uncertain whether the blinding procedure was sufficient due to visual effects of Botox treatment, results from quality of life questionnaires need to be interpreted with caution.

There were more adverse events and serious adverse events associated with Botox treatment than BSC. Statistically significant differences were found for eyelid ptosis (3.5% vs. 0.3%), neck pain (9.0% vs. 2.7%), musculoskeletal stiffness (3.2% vs. 0.9%), muscular weakness (5.5% vs. 0.3%) and myalgia (3.1% vs. 0.9%).

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The re-submission, consistent with the previous submission, claimed that Botox was superior to BSC in terms of efficacy, and inferior in terms of safety.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The re-submission presented a stepped modelled economic evaluation (Cost Utility Analysis) based on the claim of superior efficacy of botox over BSC. This model had been updated to reflect the changed continuation criteria, and changes in the total cost of treatment.

The submission presented an ICER of between $15,000 to $45,000 per QALY based on taking individual patient headache day data from the PREEMPT trials. These data were applied to chronic migraine patients with ≥2 prior prophylactic treatments and extrapolated to 5 years duration (from 24 weeks in the trial). Utility weights from the Burden of Illness Study (BIS; EQ-5D, UK weights) study were then applied.

The model structure was the same as the previous submission, a cohort Markov model defined over six health states. There were a number of issues with the use of the transition probabilities and utilities attached to the six different health states that remained unresolved from the previous submission. The re-submission presented a new, three health state model in a sensitivity analysis, in order to address PBAC concerns about the lack of statistical power to assess the transition between six health states.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

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

The total net cost to the PBS was estimated by the submission to be between $30 - $60 million over the first 5 years.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC noted that the current re-submission requested listing for patients with chronic migraine who have inadequate response, intolerance or contraindication to at least three migraine prophylaxis medications, compared with at least two in the November 2011 submission. The PBAC agreed that the nominated comparator of best supportive care (BSC) was the appropriate comparator for the population meeting the requested restriction.

The PBAC noted that, as in the previous submission, the re-submission presented the results of the PREEMPT I and II trials and also included additional post-hoc subgroup analyses for the 'three or more prior prophylactics' subgroup. The pooled analysis of the PREEMPT data demonstrated a statistically significant difference between botulinum toxin and BSC for change in headache days in both the intention to treat (ITT) population (mean difference -1.8; 95% CI: -2.52, -1.13) and the 'three or more prior prophylactics' subgroup (mean difference -2.7; 95% CI: -3.81, -1.48). The PBAC accepted that a reduction of 2-3 headache days per month could be considered to be a clinically important benefit.

The PBAC noted that the continuation rule included in the requested restriction, requiring patients to have achieved a 50% or greater reduction from baseline in the number of headache

days per month by week 24, was more restrictive than in the previous submission. However, the PBAC considered that the criteria used for assessment of response are highly subjective and that there would be considerable risk of use outside the requested restriction in patients who are 'partial responders', who experience a reduction in headache days of less than 50% compared to baseline, as such an improvement would be likely to be judged by patients to be of clinical benefit. The PBAC was concerned that such patients would be likely to continue treatment with botulinum toxin, despite not meeting the specified continuation criteria. These concerns would be exacerbated by usage beyond the subjective initiation rules relating to the type of headache, the number of headache days and the number of previous prophylactic medicines.

The PBAC noted that the economic model presented in the re-submission had been updated to reflect the changed continuation criteria and changes in the total cost of treatment. The structure of the model is otherwise unchanged from the previous submission. The updated base model did not include any changes to parameters identified by the PBAC as being of concern in the previous submission, namely the transition probabilities, utilities, cost of migraine health states and exclusion of disutility for adverse events. However the PBAC noted that these were addressed in sensitivity analyses. The base-case incremental cost per extra quality adjusted life year gained was between $15,000 and $45,000. ICERs were less favourable when different utilities and costs of migraine health states and different adverse effect disutilities were used. Concerns about the transition probabilities are partly addressed by the presentation of an additional model of three health states, and when shorter time horizons are used.

The PBAC noted that the model extrapolated the 24-week trial data to 5 years, assumed a sustained treatment effect in responders without attenuation beyond the trial duration, and assumed that patients in whom treatment is less than its definition of response would discontinue. However, the PBAC considered that the evidence presented to support the assumption of a sustained treatment effect in responders over 5 years was limited. Furthermore, while the PBAC accepted that it was reasonable to assume that patients would not continue to undergo treatment if they did not achieve any response due to the unpleasant nature of the administration protocol, the PBAC had significant concerns regarding the likelihood that patients who experience a partial response would continue treatment. The PBAC noted that the application of the continuation rule was important in driving the modelled ICER because it reduced the trial-based incremental cost per extra quality adjusted life year gained at 24 weeks from between $105,000-$200,000 to between $15,000-$45,000, and considered that these factors contributed significant uncertainty.

The PBAC considered that the re-submission's estimates of the likely number of patients treated and financial costs to the PBS were uncertain because of underestimates in the prevalence and diagnosis of chronic migraine refractory to other prophylactics, and due to the potential for use beyond the intended population in partial responders. The PBAC noted that there was an increase in the utilisation estimates despite the tighter requested restriction.

The PBAC therefore rejected the re-submission on the basis of uncertain cost-effectiveness, due to uncertainty in the economic analysis associated with the fee to administer botulinum toxin, which is currently under review by MSAC, and the assumption that all patients experiencing less than a 50% reduction in headache days would discontinue treatment, and the extrapolation of the trial data to a 5-year time horizon with a sustained treatment effect for

responders.

The PBAC also acknowledged and noted the consumer comments on this item.

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

Allergan remains disappointed with the PBAC's decision to reject the BOTOX® Chronic Migraine re-submission application, but remains committed to continuing the research to address the remaining areas of PBAC's concern, so that BOTOX® may become available on the PBS as treatment option for patients with chronic migraine.