Public Summary Document

Product: Botulinum Toxin Type A, injection, 100 units/vial, Botox®
Sponsor: Allergan Australia Pty Ltd
Date of PBAC Consideration: July 2013

1. Purpose of Application

The re-submission requested an extension to the current Section 100 (Botulinum Toxin Program) listing to include the prophylaxis of headaches in adult patients with chronic migraine who meet certain criteria.

Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

An application to the Medical Services Advisory Committee (MSAC) for a Medical Benefits Schedule (MBS) item for injection of botulinum toxin in refractory migraine was discussed at the MSAC meeting in November 2012. MSAC provided advice to the PBAC on the cost of administration. MSAC has deferred the application for the requested MBS item to inject botulinum toxin until PBAC makes a decision regarding the corresponding PBS listing.

2. Background

The PBAC has considered two previous submissions (November 2011 and July 2012) requesting an extension to the current Section 100 (Botulinum Toxin Program) listing for botulinum toxin to include the prophylaxis of headaches in adult patients with chronic migraine who meet certain criteria. The PBAC rejected the November 2011 submission on the basis of uncertain clinical benefit and highly uncertain cost effectiveness. The PBAC rejected the July 2012 re-submission on the basis of uncertain cost effectiveness.

3. Registration Status

On 15 March 2011 Botox was registered by the TGA for the requested indication:

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

Botox is also registered by the TGA for the following indications:

- Treatment of urinary incontinence due to neurogenic detrusor overactivity resulting from a defined neurological illness (such as spinal cord injury or multiple sclerosis) and not controlled adequately by anticholinergic agents. This does not include idiopathic overactive bladder.
- Treatment of strabismus in children and adults.
- Treatment of blepharospasm associated with dystonia, including benign blepharospasm and VII nerve disorders (specifically hemifacial spasm) in patients twelve years and older.
- Treatment of cervical dystonia (spasmodic torticollis).

- Treatment of 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.
- Treatment of severe primary hyperhidrosis of the axillae.
- Treatment of focal spasticity in adults.
- Treatment of spasmodic dysphonia.
- 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
Initial treatment by a neurologist of an adult patient with chronic migraine who:

1. 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 and
2. Has experienced inadequate response, intolerance or contraindication to at least three migraine prophylactic medications.

Continuing treatment of an adult patient with chronic migraine who has been reviewed by a neurologist and is responding to treatment after 2 cycles (each cycle of 12 weeks duration). Treatment response is defined as a 50% or greater reduction from baseline in the number of headache days per month by week 24.

The PBAC agreed that administration of botulinum toxin as a pharmaceutical benefit for chronic migraine should be limited to physicians who are specialists in neurology. The PBAC considered that this requirement should be addressed by an extension to the "National Health (Botulinum Toxin Program) Special Arrangement 2011" under the *National Health Act 1953*, and that the PBS restriction itself should not specify treatment by a neurologist.

The PBAC agreed that it was appropriate to include a criterion in the restriction that medication overuse must be appropriately managed prior to treatment with botulinum toxin.

The PBAC considered that a risk of use beyond the restriction remained in patients who are 'partial responders', but noted that the re-submission had attempted to address this in its proposed risk sharing arrangement. The PBAC further considered that the invasive nature of the administration may limit use in non- and partial responders.

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 the use of certain analgesics on 10-15 days or more per month; and improve quality of life.

The re-submission proposed that the place in therapy of botulinum toxin 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 contraindicated for, the available migraine prophylactic medications.

The PBAC considered that a clinical need exists for an effective treatment for refractory chronic migraine, unresponsive to multiple oral prophylactic medications.

6. Comparator

The submission nominated best supportive care (BSC) as the main comparator, consisting of no further prophylaxis but with continuation of acute headache pain medications as required.

The nominated comparator was previously accepted by the PBAC at the July 2012 meeting as appropriate for patients who have failed at least three lines of therapy.

7. Clinical Trials

The scientific basis of the re-submission was unchanged from the previous submission, that is, post-hoc sub-group analyses of the PREEMPT trials.

Results from one additional supplementary study, Cady et al (2012), were presented in the re-submission to provide further evidence regarding the long-term continuation of treatment effect. This was a Phase IV randomised, double-blind, placebo-controlled, crossover study of 20 patients with a total duration of follow-up of seven months.

The table below details the published trials and supplementary study presented in the re-submission:

Trial ID/ First author	Protocol title/ Publication title	Publication citation
PREEMPT I 191622-079	A multicentre 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, Dodick DW, Turkel CC, *et al.* 2010. On botulinum toxin A 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 multicentre 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, Dodick DW, Aurora SK, *et al*. 2010. On botulinum toxin A for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT II trial. Cephalalgia 30 (7): 804-14

8. Results of Trials

No additional analyses from the PREEMPT trials were presented in the resubmission. The results from the PREEMPT trials as presented in the previous re-submission are reproduced 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)
≥3 prior prophylactics	231	20.0 (3.5)	−7.4 (6.6)	248	20.2 (3.9)	−4.7 (6.4)	-2.7 (−3.81, −1.48)

ITT = intention to treat; SD = standard deviation; BSC = best supportive care; CI = confidence interval

The pooled analysis showed a statistically significant difference between botulinum toxin and BSC in the number of headache days in both the ITT population (-1.8; 95% CI: -2.52, -1.13) and the three or more prior prophylactic subgroup (-2.7; 95% CI: -3.81, -1.48). The PBAC recalled that in July 2012, it was accepted that a change of two to three headache days as shown in the PREEMPT trials represented a clinically meaningful outcome.

The PBAC noted the results of Cady et al (2012) for change in headache days per month from baseline were consistent with the PREEMPT trials, but were not statistically significant.

However, the PBAC considered the trial results were of limited value, noting that the trial was small (n=19) and almost no information was available to judge its quality or assess its risk of bias.

With regard to comparative harms, as presented previously, there were more adverse events and serious adverse events associated with botulinum toxin treatment than BSC from the PREEMPT trials. 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%).

Adverse events reported in Cady et al (2012) were consistent with the PREEMPT trials.

9. Clinical Claim

The re-submission described botulinum toxin as superior in terms of comparative effectiveness and inferior in terms of comparative safety over best supportive care.

The PBAC considered this claim was reasonable, as it had in July 2012.

10. Economic Analysis

The re-submission presented a modelled cost utility analysis (CUA) based on the claim of superior efficacy. The model had been updated compared to the July 2012 re-submission, to reflect the changed continuation criteria, updated botulinum toxin administration costs (in line with MSAC advice) and inclusion of disutility for adverse events.

The model was a cohort Markov model defined over six health states. The time horizon of the model was 5 years and health outcomes used were QALYs. The base case ICER was between $15,000 - $45,000/QALY based on individual patient headache day data from the PREEMPT trials. These data were applied to chronic migraine patients with two or more prior prophylactic treatments and extrapolated to five years duration (from 24-48 weeks in the trial). Utility weights from the Burden of Illness Study (BIS; EQ-5D, UK weights) were then applied. The PBAC noted that costs of treatment for adverse events related to botulinum toxin treatment were not included in the economic model.

The PBAC recalled that it had previously expressed concerns about the transition probabilities, utility values, efficacy beyond trial duration and migraine health state costs used in the model. The PBAC noted that the updated economic model did not include any changes for these parameters in the base case. However, the re-submission presented one-way sensitivity analyses around these assumptions.

The BIS was a commissioned study that included 8,726 headache patients of whom 499 had chronic migraine. The PBAC noted that the utility values in the BIS were not specific to botulinum toxin treatment, and that the BIS study included few Australian patients. Further, health resource utilisation from the BIS which was used in the economic model may not accurately represent management of chronic migraine in Australia.

The PBAC noted the re-submission presented results from a poster by Rothrock to support continued efficacy of ongoing treatment with botulinum toxin for chronic migraine. The

PBAC considered that the results did not convincingly support the claim of long-term efficacy because the open-label, single arm, single centre design of this study meant that it is at high risk of bias. The PBAC noted that the model was sensitive to assumptions regarding the duration of botulinum toxin efficacy.

The PBAC also noted that the ICER could be substantially higher than estimated in the base case if no continuation criteria were applied.

Overall, the PBAC remained concerned about the reliability of the results of the economic evaluation because of the underlying quality of the clinical and resource utilisation evidence. The PBAC considered that the calculated base case ICER was acceptable but would only be reflected in practice if the assumptions and conditions used in the model were translated into practice.

11. Estimated PBS Usage and Financial Implications

As per the previous submission, in November 2011 and July 2012, the likely number of patients per year was estimated in the submission to be less than 10,000 in Year 5. However, the PBAC noted that the re-submission's estimates of the number of patients treated and the number of treatments were increased compared to the previous submissions.

The PBAC considered the number of patients continuing treatment may be higher than assumed by the re-submission, as headache days are a subjective outcome, and if patients perceive an improvement they may be more likely to want to continue treatment. The PBAC considered there was considerable risk of use beyond the proposed restriction in partial responders, although acknowledged that the invasive nature of botulinum toxin administration may serve to limit use in partial and non-responders.

The PBAC noted the submission's estimated total net cost to the PBS of between $30 – 60 million over the first 5 years, and is higher than the costs estimated in the previous submissions, in November 2011 and July 2012, due to the increase in the estimated number of patients and treatments compared to the previous submissions. The PBAC considered the July 2012 submission provided a better estimate of patient numbers, as it included patients initiating treatment, patients continuing treatment from previous years, and patient's re-initiating after a break in therapy. The PBAC requested the Department further clarify the expected net costs to the PBS.

Given the PBAC's concerns about the likelihood of the estimated ICER being reflected in practice, the expected difficulty in differentiating use within and beyond the intent of the restriction, and the uncertainty in the estimated PBS usage and financial implications, the Committee considered that a tighter risk share arrangement would be required than that offered in the re-submission

12. Recommendation and Reasons

The PBAC recommended extending the current Section 100 Botulinum Toxin Program listing for botulinum toxin type A to include prophylaxis of headaches in adults patients with chronic migraine who meet certain criteria, on the basis of acceptable cost-effectiveness

compared to best supportive care. To address uncertainty in the cost-effectiveness being reflected in practice, the PBAC recommended that a tighter Risk Sharing Arrangement be negotiated with the sponsor.

The PBAC considered the base case ICER of between $15,000 - $45,000was acceptable, but may not represent the true cost effectiveness of botulinum toxin treatment in clinical practice, given a number of issues with the economic evaluation including the transition probabilities, the utility values, the extrapolation of the incremental treatment effect of botulinum toxin beyond the trial duration to 5 years in the absence of supportive evidence, the assumption of perfect compliance to the continuation rule in the requested restriction, and the use of the BIS as the source of utility values and resource utilisation costs in the economic model.

As previously, the PBAC accepted that the results of the PREEMPT trials supported the claim of superior comparative efficacy and inferior comparative safety of botulinum toxin over best supportive care.

The PBAC noted the re-submission's estimates of patients treated, prescriptions and packs dispensed, and net costs to the PBS/MBS were higher than in previous submissions. The PBAC considered the estimates to be uncertain due to the reasons identified during consideration of the November 2011 submission.

The PBAC acknowledged that a clinical need exists for an effective treatment for patients with chronic migraine refractory to oral prophylactic treatments. The PBAC noted and welcomed the input received from individuals (49), health care professionals (3) and patient support organisations (1) via the Consumer Comments facility on the PBS website. Most notably, comments cited reduced pain levels, improvement in quality of life and increased ability to function as benefits associated with treatment with botulinum toxin.

The PBAC considered that botulinum toxin remains unsuitable for inclusion in the list of PBS medicines for prescribing by nurse practitioners.

In accordance with subsection 101 3BA of the *National Health Act 1953*, the PBAC advised that it is of the opinion that, on the basis of the material available to its July 2013 meeting, botulinum toxin type A purified neurotoxin complex should not be treated as interchangeable on an individual patient basis with any other drug or medicinal preparation.

Outcome:
Recommended

Recommended listing
To be finalised

Name, Restriction, Manner of administration and form		Pack Size	Proprietary Name and Manufacturer	
BOTULINUM TOXIN TYPE A PURIFIED NEUROTOXIN COMPLEX Lyophilised powder for I.M. injection 100 units		1	Botox	Allergan
Condition:	Chronic migraine			
Criteria for availability:	Section 100 (Botulinum Toxin Program)			

Clinical criteria:	Patient must have 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, prior to commencement of treatment with botulinum toxin. AND Patient must have experienced an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications prior to commencement of treatment with botulinum toxin. AND The patient must have achieved and maintained a 50% or greater reduction from baseline in the number of headache days per month after two treatment cycles (each of 12 weeks duration) in order to be eligible for continuing PBS-subsidised treatment.
Population criteria:	Patient must be an adult.
Prescriber instructions:	Prophylactic migraine medications are propranolol, amitriptyline, methysergide, pizotifen, cyproheptadine or topiramate. Medication overuse must be appropriately managed prior to initiation of treatment with botulinum toxin.
Administrative Advice	Note Special pricing arrangements apply.

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 had no comment.