**PUBLIC SUMMARY DOCUMENT**
**Product:** Botulinum toxin type A purified neurotoxin complex, lyophilised powder for I.M injection, 100 units, Botox®
**Sponsor:** Allergan Pty Ltd
**Date of PBAC Consideration:** November 2011

## 1. Purpose of Application

The submission sought to extend the current Section 100 listing (Botulinum Toxin Program) to include the prophylaxis of headaches in an adult patient with chronic migraine who meets certain criteria.

## 2. Background

Botulinum toxin type A had not been previously considered by the PBAC for this indication.

## 3. Registration Status

Botulinum toxin type A was registered by the TGA 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).

## 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 of which at least 8 days are with migraine, over a period of at least 6 months
2. Prior failure or intolerance to at least two migraine prophylactic medications, which should include topiramate for patients eligible for PBS-subsidised treatment with topiramate.

Failure of oral prophylaxis is shown by persistence of 15 headache days per month of which at least 8 days are with migraine after a trial of at least 3 months duration, unless the patient experiences intolerance of a severity necessitating permanent withdrawal from treatment.
Details of the prior medication failures or intolerance(s) must be documented in the patient's medical records when treatment is initiated.
Treatment should be discontinued if the patient does not respond after two treatments. Treatment response is defined as a 30% or greater reduction from baseline in the number of headache days per month.
Patients failing to meet the continuation criteria must have a 12-month break from treatment and can then re-trial therapy once providing the initiation criteria are met.

*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 to provide initial treatment to patients who have failed the available oral migraine prophylactics and continuing treatment to patients who obtain measurable improvement by 24 weeks.

## 6. Comparator

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

The PBAC considered that the nominated comparator was not appropriate and that third-line prophylactic treatment options would be a more appropriate comparator.

## 7. Clinical Trials

The submission presented two randomised trials, PREEMPT I and PREEMPT II, as well as a pooled-data analysis, comparing botulinum toxin type A with BSC in patients with chronic migraine. Chronic migraine was defined as 15 or more headache days per month, of which at least eight are with migraine.

The key outcome measures from the trials were mean change from baseline in number of headache episodes (PREEMPT I) and mean change from baseline in headache days (PREEMPT II).

Details of the studies published at the time of submission are shown in the following table:

| Trial ID/First author | Protocol title/Publication title | Publication citation |
|---|---|---|
| PREEMPT I (191622-079) | | |
| 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) | | |
| Diener HC et 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) | | |

| Trial ID/First author | Protocol title/Publication title | Publication citation |
|---|---|---|
| Dodick DW et 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

***Comparative effectiveness***

The results for the primary outcomes from the PREEMPT trials, change from baseline in headache days per 28 days and headache episodes per 28 days at week 24, across the direct randomised trials are presented in the following table:

**Change from baseline in headache days per 28 days and headache episodes per 28 days at week 24 across the direct randomised trials**

| Trial | Botulinum toxin type A Mean (SD) | | | BSC mean (SD) | | | Mean difference (95% CI) |
|---|---|---|---|---|---|---|---|
| | N | Baseline | Change | N | Baseline | Change | |
| **Change from baseline in headache days at week 24 (Primary outcome PREEMPT II)** | | | | | | | |
| PREEMPT I | 341 | 20.0 (3.7) | - 7.8 (6.6) | 338 | 19.8 (3.7) | -6.4 (6.7) | **-1.4 (-2.4, -0.40)** |
| PREEMPT II | 347 | 19.9 (3.6) | -9.0 (6.5) | 358 | 19.7 (3.7) | -6.7 (6.7) | **-2.3 (-3.25, -1.31)** |
| Pooled | 688 | 19.9 (3.7) | -8.4 | 396 | 19.8 (3.7) | -6.6 | **-1.8 (-2.52, -1.13)** |
| **Change from baseline in headache episodes at week 24 (Primary outcome PREEMPT I)** | | | | | | | |
| PREEMPT I | 341 | 12.3 (5.2) | - 5.2 (5.2) | 338 | 13.4 (5.7) | -5.3 (5.9) | 0.1 (-1.12, 0.39) |
| PREEMPT II | 347 | 12.0 (5.3) | - 5.3 (5.3) | 358 | 12.7 (5.3) | -4.6 (4.8) | **-0.7 (-1.65, -0.33)** |
| Pooled | 388 | 12.2 (5.3) | - 5.2 | 396 | 13.0 (5.5) | -4.9 | **-0.3 (-1.17, -0.17)** |

BSC=best supportive care, CI = confidence interval, SD = standard deviation

The results from the pooled analysis of the PREEMPT I and PREEMPT II trials showed that both botulinum toxin type A and BSC demonstrated a large reduction in the number of headache days at week 24 compared to baseline (-8.4 and -6.6 days respectively). Botulinum toxin type A was associated with a statistically significantly greater reduction from baseline in headache days, mean difference -1.8 [95% CI: -2.52, -1.13].

Botulinum toxin type A was also associated with a statistically significantly greater reduction from baseline in headache episodes at week 24, mean difference -0.3 [95% CI: -1.17, -0.17].

The results of the post-hoc subgroup analysis of patients who had a history of treatment with at least one prior prophylactic medication demonstrated that botulinum toxin type A was associated with a statistically significantly greater reduction from baseline in headache days, mean difference -2.29 [95% CI: -3.15, -1.13].

Post hoc analyses of the PREEMPT trials were also conducted to determine the proportion of patients in both the botulinum toxin type A and BSC arms that achieved a response defined as

greater than or equal to a 30% reduction in total headache days. Comparisons were made with alternative definitions of response, firstly a greater than or equal to 50% reduction in total headache days and secondly a greater than or equal to 50% reduction in moderate to severe headache days and/or a greater than or equal to 30% reduction in headache days. Analyses were conducted for the total PREEMPT population and subgroups of patients with history of two or more prior prophylactic treatments.

The difference between botulinum toxin type A and BSC response was largest in patients who were pre-treated with at least two prophylactics. However, it should be noted that increasing risk difference in the more heavily pre-treated population was driven more by a reduction in the BSC response rather than by increasing probability of response to botulinum toxin type A.

*For PBAC's view of these results, see Recommendation and Reasons.*

A summary of the adverse events reported in the PREEMPT trials through week 24 and for the pooled data analysis showed that the botulinum toxin type A arms of both trials were associated with more adverse events and serious adverse events than the BSC arms. These differences were statistically significant using the pooled data. Botulinum toxin type A treatment was associated with statistically significantly greater incidence of eyelid ptosis, neck pain, musculoskeletal stiffness, muscular weakness and myalgia compared to the BSC treatment group. Additionally, although not statistically significant, botulinum toxin type A was associated with a numerically larger incidence of headache and migraine adverse events than the BSC arm. The clinical trial publications indicate that most adverse events were mild or moderate in severity and resolved without sequelae.

The submission provided further safety data derived from: two Phase-2 studies in patients with chronic migraine but using a differential dose, seven exploratory Phase-2 studies in patients with episodic migraine as well as a summary of adverse events reported within the last periodic safety update review of licensed and unlicensed indications for botulinum toxin type A. The submission stated the nature of adverse events observed in patients with chronic migraine was consistent with the known safety and tolerability profile of botulinum toxin type A with multiple injections to the head and/or neck area.

## 9. Clinical Claim

The submission described botulinum toxin type A as superior in terms of comparative effectiveness and inferior in terms of comparative safety over BSC for the prophylactic treatment of chronic migraine.

The PBAC considered that the claim of superior comparative effectiveness was not reasonable, however the claim that botulinum toxin type A is inferior in terms of comparative safety was reasonable.

## 10. Economic Analysis

The submission presented a stepped economic evaluation.

Transition probabilities across six headache-day defined health states from a post-hoc subgroup analysis of patients with ≥2 prior prophylactic treatments were used within the economic model to determine the reduction in headache days.

The submission estimated that botulinum toxin type A compared to BSC treatment in patients with chronic migraine, having failed two prior prophylactic treatments, resulted in an ICER of between $15,000 and $45,000 per QALY. The PBAC considered that this was as a result of an assumed continuous efficacy of botulinum toxin type A treatment in the model.

*For PBAC's view, see Recommendation and Reasons.*

## 11. Estimated PBS Usage and Financial Implications

The net financial cost/year to the PBS was estimated by the submission to be between $10 - $30 million in Year 5. The estimate was considered uncertain.

## 12. Recommendation and Reasons

The PBAC noted that currently only certain medical specialities may be authorised to prescribe botulinum toxin type A. The PBAC noted the advice in the sponsor's Pre-Sub-Committee Response that the Faculty of Pain Medicine has chosen not to apply for authorisation for pain specialists to prescribe botulinum toxin at this time, and that prescribing of botulinum toxin type A for chronic migraine would be limited to neurologists, who are currently authorised prescribers for botulinum toxin type A for other indications.

The PBAC considered that the nominated comparator of best supportive care (BSC), consisting of no further prophylaxis but use of acute headache pain medications as required, was not appropriate and that third-line prophylactic treatment options would be more a appropriate comparator. As the requested listing specified use of botulinum toxin type A after failure or intolerance to at least two migraine prophylactic agents, and given that more than two prophylactic treatments are available, the PBAC considered that it was more appropriate to compare botulinum toxin type A to other prophylactic treatment. It is also likely that other oral prophylactic treatments would be tried as third line and that botulinum toxin type A may be more likely to be reserved for last line use.

The PBAC noted the results from the pooled analysis of the PREEMPT I and PREEMPT II trials showed that both botulinum toxin type A and BSC demonstrated a large reduction in the number of headache days at week 24 compared to baseline (-8.4 and -6.6 days respectively). Botulinum toxin type A was associated with a statistically significantly greater reduction from baseline in headache days, mean difference -1.8 [95% CI: -2.52, -1.13]. Botulinum toxin type A was also associated with a statistically significantly greater reduction from baseline in headache episodes at week 24, mean difference -0.3 [95% CI: -1.17, -0.17]. The PBAC noted that no minimum clinically important difference (MCID) in either of these outcome measures was specified within the PREEMPT trials. The PBAC noted the large placebo effect in both PREEMPT trials and considered that the benefit of botulinum toxin type A compared to BSC was small, and is likely to be of borderline clinical significance. The PBAC considered that the MCID was unlikely to be as low as -1.8 headache days or -0.3 headache episodes, particularly given the large BSC response compared with baseline is taken into consideration.

The PBAC noted that prior prophylactic treatment was not an inclusion criterion for the PREEMPT trials, and that the results of a post-hoc subgroup analysis of patients who had a history of treatment with at least one prior prophylactic medication demonstrated that botulinum toxin type A was associated with a statistically significantly greater reduction from baseline in headache days, mean difference -2.29 [95% CI: -3.15, -1.13]. The PBAC noted

that this subgroup was not required to have failed two previous prophylactic treatments and therefore considered that these results may not be applicable to the requested PBS population which requires failure of at least two migraine prophylactic medications. Therefore, the PBAC considered that the claim of superior comparative effectiveness is not reasonable.

From the pooled results, the PBAC noted that botulinum toxin type A was associated with statistically significantly more adverse events, and serious adverse events than BSC. The PBAC considered that the claim the botulinum toxin type A is inferior in terms of comparative safety is reasonable.

The PBAC noted the stepped economic evaluation produced a base case incremental cost per extra quality adjusted life year (QALY) gained of between $15,000 and $45,000. The results of univariate sensitivity analyses presented in the submission indicated that the ICER is most sensitive to the duration of the model, transition probability estimates, the source of utility values and the comparative efficacy results used.

The PBAC considered the main areas of economic uncertainty were:

- the transitional probabilities are not sufficiently robust as they were derived from post-hoc subgroup analyses that are not sufficiently powered to assess the transition between six separate health states;
- extrapolation from 48 weeks to 5 years is uncertain as a continued effect of botulinum toxin type A is highly uncertain;
- the utilities from the Burden of Illness Study (BIS) estimated from patient data, may overestimate the incremental benefit associated with moving between the health states.

The PBAC also noted that model did not include adverse events, or the option to retrial botulinum toxin type A after 12 months, further adding to the uncertainty in the ICER and that including these in the model was likely to increase the ICER.

The PBAC considered that there was considerable uncertainty regarding the submission's estimates of usage insofar as the prevalence of chronic migraine, the rate of diagnosis of chronic migraine, and the proportion of neurologists who can administer botulinum toxin type A were all likely underestimated. The PBAC also considered that there was likely to be a considerable risk of leakage of botulinum toxin type A into other off-label chronic headache indications, use in patients who have not failed therapy and for it to be used for its cosmetic effects.

The PBAC therefore rejected the submission on the basis of uncertain clinical benefit and high and highly uncertain cost effectiveness.

The PBAC also acknowledged and noted the consumer comments received in its consideration of 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 believes that there is significant unmet clinical need in refractory chronic migraine and will work with the PBAC to make this treatment available for patients on the PBS.