Australian Government

Medical Services Advisory Committee

Public Summary Document

Application 1168 – Injection of BOTOX® (botulinum toxin type A) for prophylaxis of headaches in adults with chronic migraine

Sponsor/Applicant/s: **Allergan Australia Pty Ltd**

Date of MSAC consideration: **29 – 30 November 2012**

1. Purpose of application

In February 2011, an application to the Medical Services Advisory Committee (MSAC) was received from Allergan Australia Pty Ltd for injection of botulinum toxin (BOTOX®) for the prevention (prophylaxis) of chronic migraine. The MSAC application is co-dependent on an application to the Pharmaceutical Benefits Advisory Committee (PBAC) for the drug component of the service (i.e. extension of the current Botulinum Toxin Program (Section 100 arrangements) so the drug is listed for prophylaxis of headaches in adults with chronic migraine who meet certain criteria).

PBAC has made two separate recommendations on BOTOX® for chronic migraine, the latest being in July 2012. PBAC rejected both applications, but the July 2012 submission meets criteria for independent review.

This application was lodged during transitional arrangements for managing co-dependent PBAC/MSAC applications, so was not assessed during a joint sitting of those committees (which is now the approved process). Although PBAC rejected the drug component of this application (further detail provided under Section 2), it is seeking information from MSAC on the MBS fee for delivering the drug, consultation fee required to assess and re-assess each patient, patient out-of-pocket costs and Extended Medicare Safety Net (EMSN) risk.

Injection of botulinum toxin type A purified neurotoxin complex (BOTOX®), lyophilised powder 100 units, for prophylaxis of headaches in adults with chronic migraine. The recommended dose is 155 units to 195 units, with injections divided across seven specific head and neck areas, and including fixed-site, fixed-dose injections at 31 sites, totaling 155 units and up to an additional 40 units to eight 'follow the pain' sites. The drug is administered using a 30-gauge, 0.5 inch needle as 0.1 mL (5 units) injections per site.

Prophylaxis of headaches in adults with chronic migraine (defined as headaches on at least 15 days per month, with at least 8 days with migraine). Chronic migraine is a sub-type of chronic daily headache.

2. Background

This is the first time MSAC has considered this medical service. However, PBAC has considered funding of the drug for chronic migraine on two separate occasions, both of which have been unsuccessful. Most recently (July 2012), PBAC rejected the re-submission of BOTOX® for migraine on the basis of:

- Uncertain cost-effectiveness, due to uncertainty associated with the MBS fee to administer the drug;
- The assumption that all patients experiencing less than a 50% reduction in headache days would discontinue treatment; and
- Extrapolation of the trial data to a 5-year time horizon with a sustained treatment effect for responders.

The Therapeutic Goods Administration (TGA) has approved and registered BOTOX® for chronic migraine, which was the first chronic migraine prophylaxis agent to be specifically evaluated by the TGA.

3. Prerequisites to implementation of any funding advice

TGA approved BOTOX® for the 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) on 15 March 2011.

4. Proposal for public funding

Group T11 – Botulinum toxin **Division 2.42A of the General Medical Services Table**
• **MBS item no: TBA (within Group T11)**
• BOTULINUM TOXIN (Botox), injection of, for the prophylaxis of headaches in adults with chronic migraine who have failed at least three migraine prophylactic medications, in accordance with supply of the drug under instrument PB 122 of 2008 (Arrangements – Botulinum Toxin Program) made under Section 100 (1) (b) of the *National Health Act 1953*.
• (See para T11.1 of explanatory notes to this Category)
• **Fee:** $122.50 (proposed by applicant)

Services would be restricted to patients with headaches on at least 15 days per month, with at least 8 of those days with migraine. The recommended re-treatment schedule is every 12 weeks, but patients should not receive more than 3 cycles of treatment prior to an assessment of the need for further treatment.

MSAC ESC considered it appropriate to restrict the service to patients with chronic migraine, but agreed the diagnosis of chronic migraine (CM) as distinct from episodic migraine (EM) is not straightforward due to the inherently subjective nature of headache and symptom assessment. If a patient has a symptom score just under the 8 day threshold, this could be easily modified to meet the arbitrary criteria for receiving BOTOX® therapy, even though by definition, the patient may have EM, not CM.

Patients must have failed at least three migraine prophylactic medications. This is more restrictive than the TGA approval, but is consistent with the proposed PBS listing.
As patients are required to have failed at least three migraine prophylactic medications, MSAC ESC clarified that BOTOX® should only be considered as a fourth-line treatment option, not a third-line treatment as specified in the Final Decision Analytic Protocol (DAP).

TGA product information recommends patients should be evaluated by a neurologist or pain management specialist prior to receiving treatment (due to difficulties involved in diagnosing chronic migraine).

The SBA report indicated that the Faculty of Pain Medicine has chosen not to apply for accreditation for delivering the service at this time, meaning administration of the drug would be limited to neurologists (mainly in out-patient or consulting room settings). The DAP indicated other practitioners (including plastic surgeons and general practitioners) currently administer BOTOX® for chronic migraine. Workforce issues may necessitate that neurologists perform the initial diagnosis and prescription, but other specialists may perform subsequent injections. These specialists would need to seek approval and registration under the Botulinum Toxin Program in order to deliver a Medicare-funded BOTOX® service. MSAC ESC agreed that the diagnosis and delivery of injections should be performed by appropriately trained neurologists, who are specifically approved and registered under the Botulinum Toxin Program (Section 100 Arrangements).

5. Consumer Impact Statement

The SBA report stated that listing BOTOX® on the PBS and MBS for migraines would allow refractory (non-responsive) patients (who have no alternative treatment option) access to a safe and efficacious prophylactic treatment. The SBA report stated that prophylaxis of headaches in patients with chronic migraine using BOTOX® has been found to reduce the frequency and severity of headache days and episodes, and reduce the duration of headaches, ultimately leading to improved quality of life for patients.

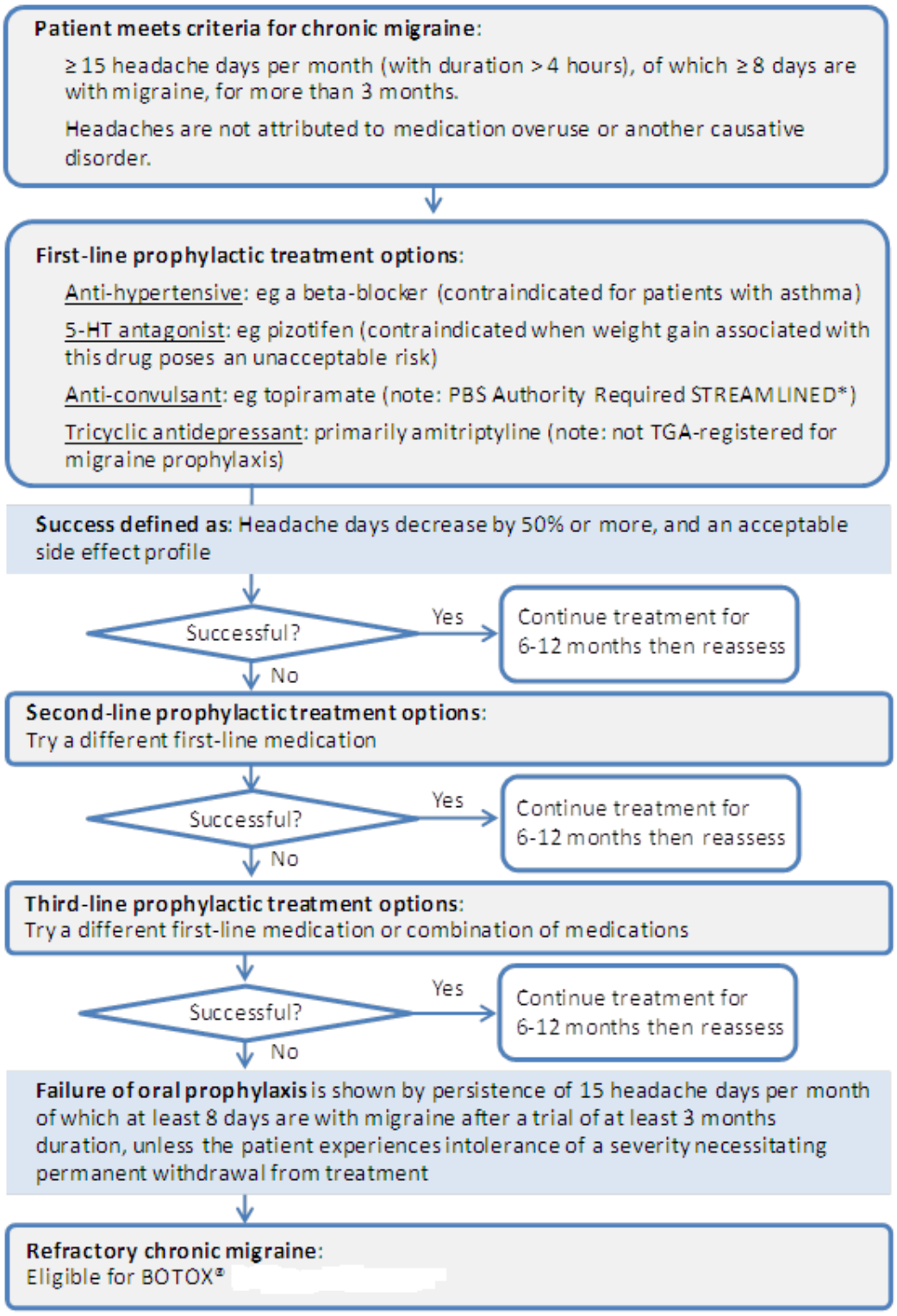
The service will be provided by specialists (in this case, neurologist) who are specifically approved and registered under the Botulinum Toxin Program. This necessary requirement will limit the number of approved specialists, with possible access issues for rural patients. However, being an out-of-hospital service, rural access may be better than if the service was provided in hospital, as well as benefitting patients without private health insurance.

No comments were received from the applicant or professional bodies on the Consultation DAP. One response was received from a consumer group, making the following comments in support of the clinical need and public health significance of the proposed service:

- chronic migraine is a common type of persistent pain;
- many patients have tried a variety of medications and non-medical strategies to try to reduce migraine incidence or intensity. It is rare for all the pain to be alleviated by current treatments; and
- botulinum toxin should be made available at the secondary and tertiary health levels to treat intractable chronic migraine. It should not be viewed as a first line therapy.

6. Proposed intervention's place in clinical management

There is no current alternative treatment on the MBS. This would be an additional intervention on the MBS. Best supportive care is available where other treatments have failed (i.e. where patients have not responded to migraine-prophylactic medications).



[source: Page 49 of SBA report]

7. Other options for MSAC consideration

MSAC PASC did not present any other options for MSAC to consider, other than aligning the MSAC recommendation to the PBAC recommendation (including applying the same patient restrictions to the MBS service that would be applied to prescription of the drug – i.e. patients must have failed at least three migraine prophylactic medications).

MSAC ESC considered the risk of leakage of the service to other indications to be low, as the proposed listing requires patients to have failed at least three migraine prophylactic medications and have the service performed by a neurologist.

8. Comparator to the proposed intervention

This service is currently not publicly funded, so there is no MBS comparator. The SBA report nominated 'best supportive care' as the appropriate main comparator. This consisted of no further prophylaxis, but continuation of acute headache pain medicines as required. The main arguments provided in support of this comparator were that patients identified within the proposed restrictions have failed to respond to, or are unable to tolerate, treatment with the available migraine prophylaxis options. BOTOX® would not be a substitute for other prophylaxis therapy.

The Final DAP nominated "best current practice, i.e. 1st and 2nd line prophylactic pharmaceuticals" as the comparator for patients who fail or experience inadequate improvement with 1st and 2nd line agents. It accepted that "failure" and "inadequate improvement" with these agents would be defined by MSAC PASC during its determination. Given the revised circumstances in which the drug is being re-assessed by PBAC (as an option following the failure of three prophylactic medications), the Critique of the SBA considered that the new comparator is more appropriate.

The Critique of the SBA report considered that, although best supportive care as a comparator is more relevant to the potential pharmacological benefits of the drug, it is also appropriate in terms of the MSAC potential listing of a service to inject the drug. The safety and effectiveness of injecting the drug is compared against a scenario of no injection, together with the financial implications to the MBS of a new listing.

In its July 2012 assessment of the re-submission BOTOX® for chronic migraine, 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 initial submission to PBAC (November 2011). PBAC agreed that the nominated comparator of best supportive care (BSC) was the appropriate comparator for the population meeting the requested restriction.

MSAC ESC agreed BOTOX® therapy would be an alternative to BSC (in patients who have inadequate response, intolerance or contraindication to at least three migraine prophylaxis medications).

This will mainly be an MBS out-of-hospital procedure, performed in doctors' private rooms. It may be provided on an in-hospital basis, but expected rates are difficult to predict, and will likely be low.

Even though some practitioners may currently be billing MBS consultation items to provide this service, this billing behavior is impossible to identify, as the activity is masked by the vast range of other services provided under consultation items that are not recorded by Medicare (Department of Human Services).

9. Comparative safety

The majority of evidence on comparative safety of the treatment was focused on the drug component which is subject to assessment by PBAC. MSAC ESC determined that the injection method to deliver BOTOX® for migraine appears no more or less safe than the injection method to deliver BOTOX® under existing MBS-listed items to administer BOTOX® for hemifacial spasm (items 18350 and 18351) and blepharospasm (items 18372 and 18373). No further matters were identified for MSAC consideration, such as whether the safety of the drug varies by the competency of the person injecting it.

10. Comparative effectiveness

The majority of the evidence on comparative effectiveness of the treatment related to the drug component is subject to assessment by PBAC. MSAC ESC determined that the injection method to deliver BOTOX® for migraine appears no more or less effective than the injection method to deliver BOTOX® under existing MBS-listed items to administer BOTOX® for hemifacial spasm (items 18350 and 18351) and blepharospasm (items 18372 and 18373).

MSAC ESC also noted that the clinical significance of a reduction of even 2 headache days per month should not be excluded. This reduction may be significant for patients who have severe, long-lasting migraines.

No further matters were identified for MSAC consideration, such as whether the clinical effectiveness of the drug varies by the competency of the person injecting it.

11. Economic evaluation

The SBA report did not present an economic evaluation of the cost-effectiveness of BOTOX® treatment for chronic migraine, as this issue was to be considered by PBAC. However, financial implications for the MBS as a result of a positive listing were examined.
Section D of the SBA report was mainly confined to providing an analysis of the time that a specialist would take to provide a service, together with estimation of the cost of this time. In the SBA report, the applicant concurred with MSAC PASC's determination that 20 minutes is an appropriate amount of time spent with a patient to deliver the injection service. However, the applicant proposed a higher fee for the service than that determined by MSAC PASC, based on an hourly rate for a specialist service derived from the Workers Compensation Regulatory Authority (in the absence of other data) adjusted downwards to align with an existing MBS item fee ($122.50). The SBA report stated this fee was more appropriate than that proposed by MSAC PASC ($74.10, based on existing MBS item 116), giving as its reason that the lower the MBS fee is, the larger the patients' out-of-pocket costs will be. MSAC may wish to consult more widely on appropriateness of the Decision Analytic Protocol-proposed fee ($74.10) versus the higher applicant-proposed fee in the SBA. Both the lower MSAC PASC-determined fee ($74.10) and a higher fee of $160.70 were tested in the sensitivity analysis.

The SBA report stated (and expert clinical opinion confirmed) that a small number of specialists currently inject BOTOX® for migraine prevention in some patients. The patient is required to pay for the drug and professional service fee. Some practitioners may be billing MBS professional attendance items for the service (for example, MBS consultant physician follow-up attendance item 116, with an MBS fee of $74.10), but these professional attendance items are generic MBS items for a wide range of practitioners and services, meaning data does not exist on individual practices under these items. The SBA report noted that, in some instances, self-pay arrangements result in a total dose no greater than 100 units (one vial) being administered in order to minimise cost. It is stated that this total dose is less than that been used in Phase III trials and less than the TGA-approved dose.

MSAC PASC had determined that the appropriate fee for the injection of the drug should be modelled on a consultant physician MBS item 116, as a 20 minute service. The fee for this item is $74.10 of which $55.60 is payable for a 75% rebate and $63.00 payable for 85%.

The MBS fee nominated in the proposed item descriptor (in the SBA report) is higher at $122.50. Although not explicitly stated, it is assumed that the equivalent rebates would be $91.90 (75% in-patient rebate) and $104.15 (85% out-patient rebate). The SBA report stated that the fee of $74.10 is "too low to cover the cost of the service to the neurologist for administering BOTOX® for chronic migraine prophylaxis. Listing BOTOX® for chronic migraine on the MBS at a fee that is considered too low may result in large co-payments to the patients." Justifications, using costing-

analyses and set out below, were provided for stating that the appropriate fee should be in the range of $133.30–$186.70, although the proposed fee is adjusted downwards from this and set at $122.50.

It was considered that the determination of an appropriate fee for this item would be a key consideration for MSAC and for the Department of Health and Ageing, and that the final fee will have a significant impact on MSACs consideration of the financial impact of the proposed new service.

MSAC ESC agreed a fee of $122.50 was appropriate, noting it would be consistent with the fee for other MBS items for administering botulinum toxin into areas of the face (i.e. injection of BOTOX® for hemifacial spasm - items 18350 and 18351 and blepharospasm - items 18372 and 18373).

PBAC noted that the economic model presented in the re-submission had been updated to reflect the changed continuation criteria, a reduced price for botulinum toxin and reduced costs of botulinum toxin administration. The structure of the model was otherwise unchanged from the previous submission. The updated base model did not include any changes to parameters identified by 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, PBAC noted that these were addressed in sensitivity analyses. The base-case incremental cost per extra quality adjusted life year gained was **(redacted information) (redacted information)** 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 were partly addressed by presentation of an additional model of three health states, and when shorter time horizons were used.

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, PBAC considered that the evidence presented to support the assumption of a sustained treatment effect in responders over 5 years was limited. Furthermore, while 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, PBAC had significant concerns regarding the likelihood that patients who experience a partial response would continue treatment. PBAC noted that 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 **(redacted information)** between $105,00 - $200,000 to between $15,00 - $45,000, and considered that these factors contributed significant uncertainty.

In the SBA report, the applicant proposed a higher MBS fee for the service than that determined by MSAC PASC (presented in the Decision Analytic Protocol). The applicant's proposed fee was based (in the absence of other data) on an hourly rate for a specialist service derived from the Workers' Compensation Regulatory Authority, adjusted downwards to align with an existing MBS item fee ($122.50). In the SBA report, the applicant stated this fee is more appropriate than the fee proposed by MSAC PASC ($74.10, based on existing MBS item 116 for a 20 minute consultant physician service), giving as its reason that the lower the

MBS fee is, the larger the patients' out-of-pocket costs will be.

PBAC considered that there was a high degree of uncertainty regarding the proposed MBS fee of $74.10 (compared with the applicant's proposed fee) for each administration of BOTOX® used in the economic model, which also contributed to uncertainty of the ICER (incremental cost-effectiveness ratio). Therefore, PBAC sought advice from MSAC regarding the fee for administering BOTOX® in the treatment of chronic migraine, in addition to the long consultation fee that is likely to be required to assess and re-assess each patient and implications for out-of-pocket payments and Extended Medicare Safety Net risk when medical practitioners will be charging patients more than the MBS fee.

PBAC considered that the re-submission 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. PBAC noted that there was an increase in the utilization estimates, despite the tighter requested restriction, **(redacted information) (redacted information) (redacted information) (redacted information).** PBAC therefore rejected there-submission on the basis of certain cost-effectiveness, due to uncertainty in the economic analysis associated with the fee to administer BOTOX®, the assumption that all patients experiencing less than a 50% reduction in headache days would discontinue treatment, and extrapolation of trial data to a 5-year time horizon with a sustained treatment effect for responders.

Expert clinical opinion was that it is difficult to know what practitioners are billing patients for the service, given the low numbers of practitioners who are doing so. As well as neurologists, expert clinical opinion was that plastic surgeons, del matologists and general practitioners in cosmetic clinics (i.e. cosmetic surgeons) would be providing the majority of services. If neurologists are billing the service to the MBS, they would be billing a subsequent consultant physician item 116, with an MBS fee of $74.10.

MSAC ESC considered that anecdotal evidence suggests that patient out-of-pocket costs for the se1vice would be about $400, but this would include the cost of the drug. Average fees charged under existing consultation items would be useful to inform MSAC of any additional costs incurred (these may be billed prior and following the proposed se1vice for patient assessment and re-assessment). MSAC ESC also noted that the MBS listing of the se1vice may result in an initial spike in referral rates.

However, MSAC ESC agreed that the proposed inte1vention should be prevented from being billed on the same occasion (same day) as a professional attendance item (e.g. MBS consultation items 110 and 116).

In the absence of information on current billing of the service, it is difficult to determine the need for capped benefits under the Extended Medicare Safety Net (EMSN).

MSAC ESC agreed that consideration should be given to placing an EMSN benefit cap on the proposed MBS item, and requested additional information on out-of-pocket costs patients are currently incurring under existing similar MBS items (for injection of BOTOX® into head, neck and facial areas; i.e. MBS hemifacial spasm items 18350 and 18351; and MBS blepharospasm items 18372 and 18373). MBS data on other items currently being claimed with these items would also assist MSAC in establishing any additional costs that may be incurred.

12. Financial/budgetary impacts

There is no MBS comparator for the service. Expert clinical opinion was that there are few Australian neurologists (perhaps two per capital city) who currently treat migraine with Botox. Expert clinical opinion is that more neurologists will perform the service if it is MBS and PBS listed, with an estimate of one-third to one-half of all neurologists moving into migraine prevention with BOTOX®. The (most recent) 2009 Australian Institute of Health and Welfare (AIHW) Medical Labour Force information showed 374 neurologists to be practising in Australia, which calculates to an estimate of 125 to 187 neurologists who may provide private (MBS-billed) BOTOX® services for migraine prevention in the future.

After the initial injection, repeat injections are provided per patient at 12 week intervals. If, after two injections, a patient fails to respond to treatment, injections are discontinued.

In the absence of comparative MBS data, expertclinical opinion was that a neurologist would see around 10 patients per week for chronic migraine, but only 3 would be candidates for BOTOX® treatment, with repeat injections at 12 week intervals.
The Critique stated that the total number of patients likely to use the drug is dependent on an assumed initiation rate, together with application of assumed continuation from the previous year, taking into account patients who failed to respondto an initial treatment, who then re-trial it during the following calendar year **(redacted information) (redacted information).**

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 MBS was estimated by the submission to be between $5 - $10 million over the first 5 years.

[redacted]

[redacted]

[redacted]

MSAC PASC considered MBS item 116 may be a reasonable guide for a proposed MBS fee ($74.10), being a 20 minute consultant physician service. In the SBA, the applicant-proposed MBS fee of $122.50 represents a reduction from their initial proposed MBS fee of $237.35 (this higher fee aligning with existing MBS BOTOX® item 18352-cervical dystonia). The applicant reduced their proposed fee because injections for dystonia are deeper, more numerous and require electrical recordings during the procedure.

Expert clinical opinion considered $74.10 to be a reasonable MBS fee, given 20 minutes is sufficient time to perform the service and given injections for migraine are less complex than injections for other conditions. As noted above, MSAC ESC considered a fee of $122.50 appropriate, as it is consistent with existing MBS items for injecting BOTOX® into the areas of the face.

Given the low numbers of practitioners providing this service, it is difficult to obtain information on the amount they charge for the service.

MSAC ESC considered that that anecdotal evidence suggests patient out-of-pocket costs for the service would be about $400, but this would include the cost of the drug.

[redacted]

There was no information on the amount practitioners charge for the service, so it is difficult

to assess Extended Medicare Safety Net risk.

The likely utilisation and costs associated with the proposed BOTOX® listing for the prophylaxis of headaches in adults with chronic migraine were estimated using an epidemiological approach.

The Decision Analytic Protocol considered that the size of the population of episodic migraine patients, and the potential for service 'leakage' to this population, would need to be considered in the SBA report. The applicant chose not to undertake this analysis, stating there were a number of reasons why this leakage is minimal. These include:

• The long term use of BOTOX® in other neurological indications on the PBS has been consistent and predictable

• Neurologists are unlikely to prescribe BOTOX® in patients with less severe headache conditions, as it is not approved and not shown to be efficacious in these populations

• Chronic migraine and episodic migraine are distinct conditions and easy to diagnose and differentiate between

• Patients are unlikely to opt for an invasive treatment if less invasive options are available

• The Botulinum Toxin Program tightly controls access to reimbursed BOTOX®.

Administration of BOTOX® would be limited to accredited neurologists. The SBA report stated that MSAC was further safeguarded against 'leakage' due to infrastructure provided by the PBAC (i.e. limited to patients who have failed at least 3 prior prophylactics and who still have at least 15 headache days per month, of which 8 are migrainous). The PBS restriction also limits continuation of BOTOX® treatment to patients who respond after two treatments. This would further reduce the risk of use in episodic migraine.

However, the Critique determined that there is potential for 'leakage' of the item within the indication of chronic migraine. This could occur, for example, in patients who had a neurologist-confirmed diagnosis of chronic migraine, but who had not undergone a trial of three previous prophylactic medicines. Medicare (Department of Human Services) would only identify these issues during post-payment audits. Effective adherence to the continuation rules that are proposed could also be problematic, particularly given their subjective nature. These issues were not considered in the Decision Analytic Protocol, as it was finalised prior to re-submission of the drug to PBAC.

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, 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 likely be judged by patients to be of clinical benefit. 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.

Additional MBS resources required to identify eligible populations to receive this treatment (or additional resources required to deliver it) were not included in the Decision Analytic

Protocol or considered in the SBA report. The Critique expressed the view that MBS- projected costs provided in the SBA report may be underestimated in the context of MBS claims for physician consultations to confirm a diagnosis of chronic migraine. However, these MBS consultations were probably already occurring so may not be an additional cost. There may be some initial renewed referral to physicians following availability of a new MBS and PBS subsidised treatment (which required their prescription), but other MBS costs should remain the same.

The SBA report described that sensitivity analysis was conducted around the steps used to drive estimates of eligible populations, including the variable MBS fees described. The upper and lower bounds of each of these parameters are compared with the base case. Results show that, based on the model developed, estimates were sensitive to changes in variables such as the prevalence, diagnosis rate and proposed administration fees.

13. Key issues for MSAC from ESC

Main issues around the proposed eligible population for public funding and/or the proposed main comparator?

Patient Population and Utilisation

As patients are required to have failed at least three migraine prophylactic medications, MSAC ESC clarified that BOTOX® should only be considered as a fourth-line treatment option, not a third-line treatment as specified in the Final DAP.

MSAC ESC considered it appropriate to restrict the service to patients with chronic migraine, but agreed the diagnosis of chronic migraine (CM) from episodic migraine (EM) was not straight forward due to the inherently subjective nature of headache and symptom assessment. If a patient has a symptom score just under the arbitrary 8 day threshold, this could be easily modified to meet the criteria for receiving BOTOX® therapy, even though the patient may have EM, not CM.

However, MSAC ESC agreed that the risk of leakage of the service to other indications is low, as the proposed listing required patients to have failed at least three migraine prophylactic medications and have the service performed by a neurologist.

MSAC ESC noted that because the effect of BOTOX® attenuates over time, repeated

injections would be needed approximately every 3 months. Although migraine is thought to dissipate over time, there was uncertainty about how long patients would require ongoing treatment.

MSAC ESC considered that, while difficult to predict, there is potential for an initial increase in MBS professional attendances surrounding the new intervention if a specific MBS item is listed for BOTOX® for migraine. This is because patients may need to return to their GP for an updated referral, re-consult their neurologist for this alternative treatment, or consult another neurologist (if their current neurologist does not administer BOTOX®). This would only involve patients who have, up until the MBS listing, chosen not to receive the treatment in the absence of a specific MBS BOTOX® item, or for whom the option of this treatment was not considered due to the lack of widespread knowledge about this treatment. It is also important to note that MSAC ESC considered the estimates of usage contained in the SBA report to be open to change and uncertain.

Comparator

MSAC ESC agreed BSC would be the appropriate comparator.

Main issues around the evidence and conclusions for safety?

While the majority of evidence on comparative safety of the treatment was focused on the drug component (which will be assessed by PBAC), MSAC ESC determined that the injection method to deliver BOTOX® for migraine appears no more or less safe than the injection method to deliver BOTOX® under existing MBS-listed items to administer BOTOX® for hemifacial spasm (items 18350 and 18351) and blepharospasm (items 18372 and 18373).

Main issues around the evidence and conclusions for clinical effectiveness?

While the majority of evidence on comparative effectiveness of the treatment related to the drug component of this intervention (which will be assessed by PBAC), MSAC ESC determined that the injection method to deliver BOTOX® for migraine appeared no more or less effective than the injection method to deliver BOTOX® under existing MBS-listed items to administer BOTOX® for hemifacial spasm (items 18350 and 18351) and blepharospasm (items 18372 and 18373).

Other important clinical issues and areas of clinical uncertainty?

Most of these issues will be determined and resolved by PBAC, in relation to the use of BOTOX® for migraine. However, MSAC ESC noted that the clinical significance of a reduction of even 2 headache days per month should not be excluded. This reduction may be significant for patients who have severe, long-lasting migraines.

Main economic issues and areas of uncertainty?

Noting that PBAC rejected the resubmission for the drug on the basis of uncertain cost-effectiveness, MSAC was not expected to reach conclusions on economic issues. However MSAC ESC did note that for those in whom treatment works, there may be cost savings arising from less consultations with GP's and less use of medications. PBAC's role will address the economic issues, and PBAC will use information from MSAC on the appropriate MBS fee for the service (and associated MBS costs) to inform PBAC's economic assessment.

MBS Fee

MSAC ESC agreed the most appropriate MBS fee was $122.50, noting it would be consistent with the fee for other MBS items for administering botulinum toxin into areas of the face (i.e. injection of BOTOX® for hemifacial spasm - items 18350 and 18351 and blepharospasm -

items 18372 and 18373).

Patient Out-of-Pocket Costs and Extended Medicare Safety Net Risk

MSAC ESC accepted advice that patient out-of-pocket costs for the service together with the drug are currently total about $400.

MSAC ESC agreed consideration should be given to placing an Extended Medicare Safety Net (EMSN) benefit cap on the proposed MBS item, and requested additional information on out-of-pocket costs patients are currently incurring under existing similar MBS items (i.e. for injection of BOTOX® into face, head or neck areas, which also have MBS fees of $122.50 (items 18350, 18351, 18372 and 18373). The average patient co-payments under these items could be multiplied by 4 (treatments per year) to estimate the likely impact on the EMSN. Current co-claiming amounts under these items will also inform MSAC about additional costs patients are incurring.

MSAC ESC considered it appropriate to prevent a standard consultation item (i.e. 110) being billed on the same occasion (i.e. same day) as the proposed MBS item for injecting BOTOX®. This will need to be written into the item descriptor to make it clear and enforceable.

Possible other MBS costs to be considered

To inform the need for capping of EMSN benefits, as well as whether additional MBS costs would result from listing this intervention on the MBS (i.e. will a patient go back to their GP for a new referral and/or have an additional specialist consultation if BOTOX® for migraine is listed), the following data will be provided to MSAC:

1. Average fee charged for hemifacial spasm (items 18350 and 18351) and blepharospasm (items 18372 and 18373);
2. Other items being claimed in association with the above items for hemifacial spasm and blepharospasm;
3. Average fee charged for an initial specialist consultation item 110 (to determine appropriateness for injection of BOTOX® for migraine - not on same day as the injections);
4. Average fee charged for follow-up specialist item 116 (to review patient after the BOTOX® injections - not on same day as the injections);
5. Average fee charged for GP referral to specialist, under GP item 23; and
6. Average fee charged for GP referral to specialist, under GP item 36.

14. Other significant factors

Expert clinical opinion was that there may be some confusion about whether a professional attendance (standard consultation) item can be billed on the same occasion as delivering BOTOX® injections (with or without a dedicated MBS BOTOX® item). This issue could be considered in the context of the broader review of all BOTOX® items, which is currently at public consultation phase of the MSAC process.

15. Summary of consideration and rationale for MSAC's advice

MSAC noted that the application from Allergan in June 2012 preceded PBAC consideration of the associated request to extend the PBS listing of botulinum toxin to include refractory migraine in July 2012. PBAC decided not to recommend the requested listing and referred questions to MSAC for advice to be included in any resubmission from the applicant to PBAC. MSAC first considered the requests from PBAC because they

helped focus on the matters to be addressed and then considered any other matters which were relevant.

Responses to PBAC requests for MSAC advice

MSAC advised that it would support $124.85 as the MBS fee for injecting botulinum toxin in refractory migraine, with reference to the 1 November 2012 MBS fees for MBS items 18350, 18351, 18372 and 18373 as benchmarks. 18350 and 18351 are to inject botulinum toxin for hemifacial spasm; 18350 is for the Botox® brand which has the majority of the botulinum toxin market for this indication. 18372 and 18373 are to inject botulinum toxin for bilateral blepharospasm; 18372 is for the Botox® brand which has the majority of the botulinum toxin market for this indication.

MSAC advised that the consultation item(s) likely to be required to assess and reassess each patient would be MBS item 110 (noting that neurologists, who are nominated to inject botulinum toxin for migraine, are consultant physicians) for an initial assessment if referred for this purpose, and MBS item 116 for an initial assessment for this purpose (if part of the ongoing management by the neurologist, having been referred earlier) and also for subsequent reassessments. In addition, if general practitioners are to be included in the overall economic evaluation for any reason, such as for increased referral rates or for ongoing assessments, then the GP attendance item(s) likely to be required are MBS items 23 and 36.

MSAC advised that the implications for out-of-pocket payments are as set out for each identified MBS item (proposed and existing) in the tables below. Each amount is calculated as the difference between the relevant average fee charged (for the most recent financial year) and the relevant rebate in the current Schedule of Medicare Benefits. For the proposed MBS item, the average fee charged was calculated as the average fee charged by neurologists for injecting botulinum toxin (Botox® brand) for the benchmark indications of hemifacial spasm (18350) and bilateral blepharospasm (18372), weighted by the total number of services rendered for these two items. For the two consultant physician items (110 and 116), the average fee charged was calculated for the neurology specialty only (for greater accuracy).

MSAC further advised that, in the context of proposed MBS items to inject proposed PBS listings of botulinum toxin, the relative influence of MBS costs on the overall economic evaluation for the PBS proposal is greater than usual. For this reason, MSAC advised PBAC and the applicant that the average fee charged in these tables should be included in the economic evaluation to reflect its opportunity cost from the health care system perspective (rather than the MBS fee as is recommended in PBAC's Manual of Resource Items and their Unit Costs). Similarly, the relevant costs to the MBS for inclusion in the financial analyses are also provided in the table, based on the most applicable rebate (outside the hospital setting).

MSAC advised against including any consequences for the Extended Medicare Safety Net (EMSN) in the economic evaluation or the financial analysis. In support of this advice, MSAC first noted that the consultant physician and GP items identified already (110, 116, 23, and 36) have an EMSN cap, and second, foreshadowed its intention to advise that a cap should apply to the proposed MBS item for the purposes of the EMSN. Specifically, in the event of a PBAC recommendation to list botulinum toxin for refractory migraine, MSAC would revisit this matter and advise the Minister on the amount of an EMSN cap for the corresponding MBS item to inject the botulinum toxin. In this context, MSAC accepted ESC advice that the cost of the

(per injection) out-of-pocket payment should be multiplied by four to give an annual estimate. MSAC requested that the bulk billing rate and the weighted average fee charged for patient-billed items 18350 and 18372 be obtained for the most recent financial year as the basis for reconsidering the EMSN consequences at that time. MSAC further noted that the current MBS items to inject botulinum toxin are the subject of a review, which may also provide relevant information.

Item number	**Proposed item**
Brief description	Inject botulinum toxin for migraine
Fee	$124.85
Government pays (rebate)	$106.15 (85%)
Patient pays (OOP)	$4.61
Total (average fee charged)*	$110.76

* The average fee charged is less than the MBS fee because of the high rate of bulk billing. The amount charged for a bulk-billed service is the MBS rebate, not the MBS fee.

Item number	**110**	**116**	**23**	**36**
Brief description	Initial consultant physician attendance	Subsequent consultant physician attendance	GP attendance < 20 minutes	GP attendance > 20 minutes
Fee	$150.90	$75.50	$36.30	$70.30
Government pays (rebate)	$128.30 (85%)	$64.20 (85%)	$36.30 (100%)	$70.30 (100%)
Patient pays (OOP)	$42.57	$22.38	$5.04	$4.67
Total (average fee charged)	$170.87	$86.58	$41.34	$74.97

Additional MSAC considerations and rationale

MSAC advised that there was no evidence to suggest that any variation in injecting performance across trained and experienced neurologists would be likely to have important consequences for patient safety or for the effectiveness and safety of botulinum toxin in the proposed indication. MSAC decided that the overall comparative effectiveness and safety of botulinum toxin were matters for PBAC to consider.

MSAC advised that, in the event of a PBAC recommendation to list botulinum toxin for refractory migraine, it would revisit the wording of the proposed MBS item descriptor. Specifically, the Committee foreshadowed its intention to advise that the definition of eligible patients should be aligned with any PBAC-recommended PBS restriction and to consider excluding the billing of attendance items to assess or reassess the patient on the same occasion of service, especially for subsequent injections (with the proposed fee allowing time for assessing and injecting). In relation to this proposed exclusion, MSAC referred to data indicating that, of the 11,733 services rendered in 2011-12 for the benchmark MBS items

18350, 18351, 18372 and 18373, 64% had a consultant physician attendance co-claimed on the same day, and 25% had a specialist attendance co-claimed on the same day. MSAC requested that a breakdown of these co-claimed services for the most recent financial year be presented to better inform its consideration of possible exclusions at that time. MSAC agreed that assessment and reassessment were necessary aspects of managing therapy with botulinum toxin, and the frequency of these might change should botulinum toxin be funded for this

purpose, but did not consider that this should form part of the process of injection. MSAC also considered the possibility of limiting the item to appropriately trained neurologists, but accepted advice that this issue would be appropriately handled as part of any extension of the PBS arrangements for botulinum toxin.

16. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to the safety, clinical effectiveness and cost-effectiveness of the injection of botulinum toxin in the treatment of refractory migraine, MSAC deferred the application for the requested MBS item to inject botulinum toxin until such time as PBAC makes a decision regarding the corresponding PBS listing of botulinum toxin. In doing so, PBAC will take into account responses to the questions it has posed to MSAC. If PBAC refers more matters to MSAC for advice, or the applicant has reason to disagree with the advice given above, MSAC will support an expedited process for reconsideration. If PBAC subsequently decides to recommend to the Minister that botulinum toxin be listed on the PBS for the treatment of refractory migraine, MSAC will support an expedited process for reconsideration to align MSAC support for public funding of the injection of botulinum toxin according to the circumstances recommended by PBAC. The purpose of this reconsideration would be to align the proposed MBS item descriptor with the proposed PBS restriction; consider the possible exclusion of other attendance items to be billed to the patient on the same occasion of service; provide advice on the amount of any cap for the Extended Medicare Safety Net; and consider changes in the estimates of costs to the MBS.

17. Applicant's comments on MSAC's Public Summary Document

Nil.

18. Context for decision

This advice was made in accordance with MSAC Terms of Reference.

MSAC is to:

Advise the Minister for Health and Ageing on medical services that involve new or emerging technologies and procedures and, where relevant, amendment to existing MBS items, in relation to:

- the strength of evidence in relation to the comparative safety, effectiveness, cost-effectiveness and total cost of the medical service;
- whether public funding should be supported for the medical service and, if so, the circumstances under which public funding should be supported;
- the proposed Medicare Benefits Schedule (MBS) item descriptor and fee for the service where funding through the MBS is supported;
- the circumstances, where there is uncertainty in relation to the clinical or cost-effectiveness of a service, under which interim public funding of a service should be supported for a specified period, during which defined data collections under agreed clinical protocols would be collected to inform a re-assessment of the service by MSAC at the conclusion of that period;
- other matters related to the public funding of health services referred by the Minister.

Advise the Australian Health Ministers' Advisory Council (AHMAC) on health technology

assessments referred under AHMAC arrangements.

MSAC may also establish sub-committees to assist MSAC to effectively undertake its role. MSAC may delegate some of its functions to its Executive sub-committee.

19. Linkages to other documents

MSAC's processes are detailed on the MSAC Website at: www.msac.gov.au.