
1168

Final Decision
Analytic Protocol
(DAP) to guide the
assessment of the
injection of BOTOX®
for prophylaxis of
headaches in adults
with chronic
migraine.

May 2012

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MSAC and PASC

The Medical Services Advisory Committee (MSAC) is an independent expert committee appointed by the Minister for Health and Ageing (the Minister) to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister on the evidence relating to the safety, effectiveness, and cost-effectiveness of new and existing medical technologies and procedures and under what circumstances public funding should be supported.

The Protocol Advisory Sub-Committee (PASC) is a standing sub-committee of MSAC. Its primary objective is the determination of protocols to guide clinical and economic assessments of medical interventions proposed for public funding.

Purpose of this document

This document is intended to provide a draft decision analytic protocol that will be used to guide the assessment of an intervention for a particular population of patients. The draft protocol will be finalised after inviting relevant stakeholders to provide input to the protocol. The final protocol will provide the basis for the assessment of the intervention.

The protocol guiding the assessment of the health intervention has been developed using the widely accepted "PICO" approach. The PICO approach involves a clear articulation of the following aspects of the research question that the assessment is intended to answer:

Patients – specification of the characteristics of the patients in whom the intervention is to be considered for use;

Intervention – specification of the proposed intervention

Comparator – specification of the therapy most likely to be replaced by the proposed intervention

Outcomes – specification of the health outcomes and the healthcare resources likely to be affected by the introduction of the proposed intervention

Purpose of application

A proposal for an application requesting MBS listing of the injection of BOTOX® for prophylaxis of headaches for adults with chronic migraine was received from Allergan Australia Pty Ltd. by the Department of Health and Ageing in February 2011.

PASC has finalised this protocol to guide the assessment of the safety, effectiveness and cost-effectiveness of BOTOX® for prophylaxis of headaches in adults with chronic migraine in order to inform MSAC's decision-making regarding public funding of the intervention.

Intervention

Description

Description of the condition

Chronic daily headache (CDH) occurs on at least 15 days a month (Mayo Clinic, 2010). Chronic migraine (CM) is a sub-type of chronic daily headache; chronic migraine is defined as a headache on at least 15 days per month, with at least 8 headache days meeting the criteria for migraine (Olesen et al, 2006).

The literature differentiates between chronic and episodic migraine; patients with episodic migraine (EM) – commonly referred to as 'migraine' – have headache on fewer than 15 days per month. Chronic migraine is distinguished from episodic migraine not only by the number of headache days per month but also by a greater burden of illness in terms of health-related quality of life (HRQoL), co-morbid conditions and health resource use. These differences, as well as physiological data, were used by Lipton and Chu (2009) to support their argument that CM and EM should be conceptualised as distinct but related disorders.

A systematic review of quality of life studies in CDH (Lanteri-Minet et al, 2011) showed that patients with CDH have consistently worse scores across most domains of the SF-36 compared with episodic headache sufferers and normative controls. The majority of studies found that CDH sufferers with migrainous features have lower SF-36 HRQoL scores than those who do not.

The International Burden of Migraine Study (IBMS) found that CM causes significantly greater impact on HRQoL relative to EM (Blumenfeld et al, 2011). In the American Migraine Prevalence and Prevention (AMPP) study, patients suffering from CM (N=655) had significantly lower household income levels than those with EM (N=11,249), were significantly less likely to be employed full time and nearly twice as likely to be occupationally disabled (Buse et al, 2010). In the IBMS and AMPP studies, CM was associated with significantly higher rates of co-morbid conditions including anxiety, depression, obesity and cardiovascular diseases or risk factors (Buse et al, 2010; Blumenfeld et al, 2011). Additionally, patients with transformed or chronic migraine had significantly more healthcare visits including GPs, specialists, ER and hospitalisations (Munakata et al, 2009; Blumenfeld et al, 2011).

Prophylactic treatment for migraine should be considered in patients with recurring migraines that significantly interfere with their daily routine or in the presence of contraindication to, failure of, or overuse of acute therapies. The goal of preventive therapy is to reduce the attack frequency, severity and duration, improve responsiveness to treatment of acute attacks and reduce migraine associated disability (SIGN Guidelines).

Description of the intervention

Botulinum toxin (BOTOX®) is produced by the gram-positive anaerobic bacterium Clostridium; it is among the most potent biologic neurotoxins. BOTOX®'s primary mechanism of action is inhibition of acetylcholine release at the presynaptic cholinergic junction. This results in a reduction of type Ia/II intrafusal muscle fiber afferent conduction, affecting the spinal stretch reflex and decreasing muscle tone and contractility without affecting muscle strength (Smaldone et al, 2010). BOTOX®'s analgesic effects are thought to benefit patients with migraine (NHSC 2010), however, the precise mechanism of action is not yet certain.

For the prophylaxis of chronic migraine, BOTOX® is injected into multiple sites in the head and neck; no anaesthetic is required for the injections. The goal of the treatment is to reduce migraine severity and symptoms.

Administration, dose, frequency of administration, duration of treatment

BOTOX® injections are given at seven specific head and neck areas (frontalis, corrugators, procerus, occipitalis, temporalis, trapezius and cervical paraspinal) as specified in the BOTOX® product information and described by Blumenfeld et al, (2010). There are 31 fixed-site, fixed-dose injections totalling 155 U and up to an additional 40 U to eight 'follow the pain' sites corresponding to the occipitalis, temporalis and trapezius, for a total maximum dose of 195 U.

Head/Neck Area	Total Number of Units (no. of injection sites ^(a))
Frontalis ^(b)	20 U (4 sites)
Corrugator ^(b)	10 U (2 sites)
Procerus	5 U (1 site)
Occipitalis ^(b)	30 U (6 sites) up to 40 U (up to 8 sites)
Temporalis ^(b)	40 U (8 sites) up to 50 U (up to 10 sites)
Trapezius ^(b)	30 U (6 sites) up to 50 U (up to 10 sites)
Cervical paraspinal ^(b)	20 U (4 sites)

U = Units of BOTOX®; ^(a) 1 injection site = 0.1 ML = 5 U BOTOX®; ^(b) Dose distributed bilaterally for minimum dose

Repeated injections are required for this indication because the effect of BOTOX® attenuates after 2-3 months (8-12 weeks). Therefore, the proposed intervention would be given every 12 weeks / four times per year.

The pattern of migraine is highly variable, and occasionally associated with hormonal fluctuation connected to the menstrual cycle, as well as stress, diet and sleep patterns. Therefore, the patient's response to therapy should be assessed after two cycles (that is, at 24 weeks), in order to establish the benefit of BOTOX®.

Duration of delivery is based on patient response. Clinical experts noted that the benefits of BOTOX® may attenuate over several years of use in some patients. Because incidence of migraine attenuates past the age of 55, there is no need for an upper limit to the duration of use of BOTOX®.

The procedure is generally performed on patients in the office or in hospital on an out-patient basis. The Applicant proposes that the item be for delivery only by neurologists, who currently inject BOTOX® for other indications such as cervical dystonia (spasmodic torticollis).

A concern arises here about the potential for 'leakage' to other indications (e.g., episodic migraine, and cosmetic uses), should this treatment be approved. A requirement that a neurologist carry out both the diagnosis and the injections would aid in prevention of this 'leakage.' However, the Clinical Experts advised that the number of neurologists using BOTOX® for the treatment of migraine is very small, and BOTOX® is currently administered for migraine also by plastic surgeons, GPs and other doctors. Workforce issues may therefore necessitate that neurologists perform the initial diagnosis and the first two courses of treatment, and other specialists perform subsequent injections. (It needs to be emphasised here that all specialists delivering BOTOX® must be registered by Medicare Australia to participate in the arrangements under section 100 of the National Health Act 1953, relating to the use and supply of Botulinum Toxin).¹

Co-administered interventions

Patients are diagnosed as chronic migraine sufferers on the basis of an initial consultation, and a subsequent headache diary (of between 1-3 months' length). No 'objective' tests are currently available to determine whether a patient is a chronic migraine sufferer.

The health care resources required on the same day as the injection include: a consultation with a neurologist, diagnosis, BOTOX® cost, injection cost, needle cost, and cost of the syringes used for the BOTOX® injection.

¹ Currently, items for the administration of botulinum toxin can only be claimed by a medical practitioner who is registered by Medicare Australia to participate in the arrangements under Section 100 of the *National Health Act 1953* relating to the use and supply of botulinum toxin. Consistent with current practice, it is expected that only neurologists will be able to administer botulinum toxin for the proposed use. If non-neurologist administration becomes possible, PASC suggested that the patient would need to be reviewed by the initial specialist. Under this option, there would likely be a need for more than one MBS item descriptor to cover the initial assessment by the neurologist, the non-neurologist administration(s) and the subsequent review(s) by the neurologist.

Patients who are considered for BOTOX® will have failed or experienced inadequate improvement² with non-pharmaceutical and/or pharmaceutical therapy. However, some patients may remain on medications for acute attacks (NSAIDs, triptans) during the treatment with BOTOX®. Non-pharmaceutical therapies currently in use include: a regulation of diet, exercise and sleep, as well as stress management. Pharmaceutical treatment includes preventatives (beta-blockers, calcium channel blockers, anti-epileptics, serotonin modulators, antidepressants) and/or abortives (analgesics, triptans) (NHSC 2010).

Background

Current arrangements for public reimbursement

BOTOX® injection for chronic migraines is currently available to patients visiting a neurologist through self-pay; it is not presently claimable under any MBS item for this indication.

However, BOTOX® is currently reimbursed through MBS for other indications, which include:

- hemifacial spasm in a patient 12 years of age or older
- cervical dystonia (spasmodic torticollis)
- dynamic equinus foot deformity due to spasticity in an ambulant cerebral palsy patient, aged two years or older
- dynamic equinovarus foot deformity due to spasticity in an ambulant cerebral palsy patient, aged two years or older
- dynamic equinovalgus foot deformity due to spasticity in an ambulant cerebral palsy patient, aged two years or older
- the treatment of focal spasticity in adults
- the treatment of severe primary hyperhidrosis of the axillae
- the treatment of strabismus in children and adults
- the treatment of spasmodic dysphonia
- the treatment of blepharospasm in a patient 12 years of age or older
- the treatment of bilateral blepharospasm in a patient 12 years of age or older

A full listing (including the MBS item numbers) is provided in Appendix 2.

² PASC agreed that the Pharmaceutical Benefits Advisory Committee (PBAC) needs to address the issues of how to define 'inadequate improvement,' and 'therapy failure.'

As BOTOX® injection for chronic migraines is not presently claimable under any MBS item, current utilisation rates are difficult to establish.

Fee information

Allergan did not provide fee information. As noted above, however, BOTOX® injection is currently reimbursed on the MBS for a range of TGA approved indications. The fees for these items range from \$43.35 to \$256.90. Allergan advises that the most similar MBS items are 18352 for cervical dystonia (spasmodic torticollis) and 18362 for severe primary hyperhidrosis of the axillae. The fees for these items are \$240.30 and \$237.35, respectively.

Given that the injection of BOTOX® for prophylaxis of headaches in adults with chronic migraine involves injections into the head and neck muscles, MBS item 18352 (cervical dystonia, which involves injection to the head and neck areas (Walker, 2003)) appears to be more similar than MBS item 18362 (severe primary hyperhidrosis of the axillae, which involves injections to the axillae (Talarico-Filho et al, 2007)). However, PASC noted that cervical dystonia requires injections that are both deeper and more numerous, as well as requiring electrical recordings during the procedure. In terms of both complexity and time involved, the process of injection of BOTOX® for chronic migraine therefore more closely resembles the injections of BOTOX® for cosmetic purposes than those for cervical dystonia. PASC therefore agreed that the fee for the injection of BOTOX® for chronic migraine should be modelled on a consultant physician MBS item 116, as a 20 minute service.

Table 1: MBS descriptor for item 116

GROUP A4 - CONSULTANT PHYSICIAN ATTENDANCES TO WHICH NO OTHER ITEM APPLIES
MBS item 116
Each attendance (other than a service to which item 119 applies) SUBSEQUENT to the first in a single course of treatment
Fee: \$74.10 Benefit: 75% = \$55.60 85% = \$63.00

The injection of BOTOX® for prophylaxis of headache in adults with chronic migraine will require its own MBS item number, with paragraph T11.1 of explanatory notes applying. It is worth reiterating that in light of the aforementioned concerns about 'leakage' to other uses, the descriptor needs to specify strict eligibility criteria.

Table 2: Proposed MBS item descriptor for the injection of BOTOX® for prophylaxis of headaches in adults with chronic migraine.

Category 3 – THERAPEUTIC PROCEDURES

MBS [item number to be assigned by the Department if listed on the MBS]

BOTULINUM TOXIN (Botox), injection of, for the third-line prophylaxis of headaches in adults with chronic migraine, in accordance with the 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)³

Fee: \$[Proposed fee]

The TGA approved indication (TGA entries 172264 and 67311) for BOTOX® is for 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). The requested MBS listing is therefore consistent with the TGA approved indication (i.e., it is also for the prophylaxis of headaches in adults with chronic migraine, where the chronic migraine is defined as headache on at least 15 days per month, of which at least 8 days are with migraine).

Regulatory status

BOTOX® is currently TGA-approved (under TGA entries 172264 and 67311) for a number of indications, including the 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). The other approved indications (under the same entries) include:

- Treatment of urinary incontinence due to neurogenic detrusor overactivity (NDO) resulting from a defined neurological illness (such as spinal cord injury or multiple sclerosis) and not controlled adequately by anticholinergic agents
- 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 over;
- Treatment of cervical dystonia (spasmodic torticollis);
- Treatment of 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;
- Treatment of severe primary hyperhidrosis of the axillae;
- Treatment of focal spasticity in adults.
- Treatment of spasmodic dysphonia.

³ Paragraph T11.1 is provided in Appendix 2.

BOTOX (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, crows' feet and forehead lines) in adults.

An alternative clostridium botulinum type A toxin, Dysport, is also TGA-registered for a more limited list of indications. Under TGA entries 74124 and 170651 Dysport is specified for the treatment of:

- spasticity of the upper limb in adults following a stroke;
- spasmodic torticollis in adults;
- dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients, two years of age or older;
- blepharospasm in adults;
- hemifacial spasm in adults;
- moderate to severe glabellar lines in adults.

Patient population

There is a potential for the size of the population to be much larger than that proposed by the applicant, depending on how 'inadequate improvement' and 'failure' of prophylactic pharmaceuticals are defined within the clinical management algorithm. (PASC agreed that PBAC needs to address the issue of how to define these concepts.) The size of the patient population may also be increased due to the aforementioned potential for 'leakage' of the service into the episodic migraine patient population.

BOTOX® is contraindicated for the following patients: individuals with hypersensitivity to ingredients in the formulation, patients with myasthenia gravis or Eaton Lambert Syndrome, and presence of infection at the injection site. The effects of the use of BOTOX® in pregnant women are unknown, therefore BOTOX® should not be used in those patients unless the benefits clearly outweigh the risks. No information is available on whether BOTOX® is excreted in breast milk, thus the use of BOTOX® is not recommended whilst breastfeeding.

Clinical place for proposed intervention

European Federation of Neurological Societies (EFNS) guidelines state that prophylactic drug treatment of migraine should be considered and discussed with the patient when:

- the quality of life, business duties, or school attendance are severely impaired
- frequency of attacks per month is two or higher

- migraine attacks do not respond to acute drug treatment
- frequent, very long, or uncomfortable auras occur.

A migraine prophylaxis is regarded as successful if the frequency of migraine attacks per month is decreased by at least 50% within 3 months (EFNS 2009).

Based on these, or similar criteria, all patients with chronic migraine (defined as headache on at least 15 days per month, with at least 8 headache days meeting the criteria for migraine) would be considered suitable for prophylactic drug treatment. It is assumed that these patients have tried non-pharmaceutical therapies, which include: regulation of diet, exercise, and sleep, as well as stress management (NHSC 2010).

The SIGN guidelines provide the following general principles for the preventive treatment for migraine:

- most preventive drugs should be titrated slowly to an effective or maximum dose, in order to minimise side effects
- preventive medication should be given a trial of at least six to eight weeks following dose titration
- the choice of preventive medication should be guided by its side effect profile and the patient's co-morbid conditions
- after six to 12 months of effective prophylaxis, gradual withdrawal should be considered (SIGN Guidelines)

There are a wide range of pharmaceuticals for the preventive treatment of migraine; they are generally used for this indication after establishing themselves for other indications (Stark and Stark, 2008). Alongside preventive migraine treatment, patients should also have access to appropriate medications for treatment of acute attacks of migraine such as analgesics (e.g. paracetamol, NSAIDs) and triptans (serotonin I_B/I_D agonists, e.g. sumatriptan, rizatriptan, eletriptan, naratriptan and zolmitriptan).

According to the recent European Federation of Neurological Societies (EFNS) guidelines, prophylactic pharmaceuticals of first choice are:

- betablockers (metoprolol and propranolol)
- calcium channel blockers (flunarizine), and
- antiepileptics (Sodium valproate and topiramate) (EFNS 2009).

These guidelines consider the antidepressants (amitriptyline and venlafaxine) to be drugs of second choice. Each of these drugs has specific side effect profiles and choice will depend on the patient's profile of co-morbid conditions.

Recent Australian Guidelines list the following drugs as first-line options:

- Amitriptyline
- Pizotifen
- Propranolol

The following drugs are considered second-line options:

- Sodium valproate
- Topiramate
- Verapamil (Therapeutic Guidelines, 2011).

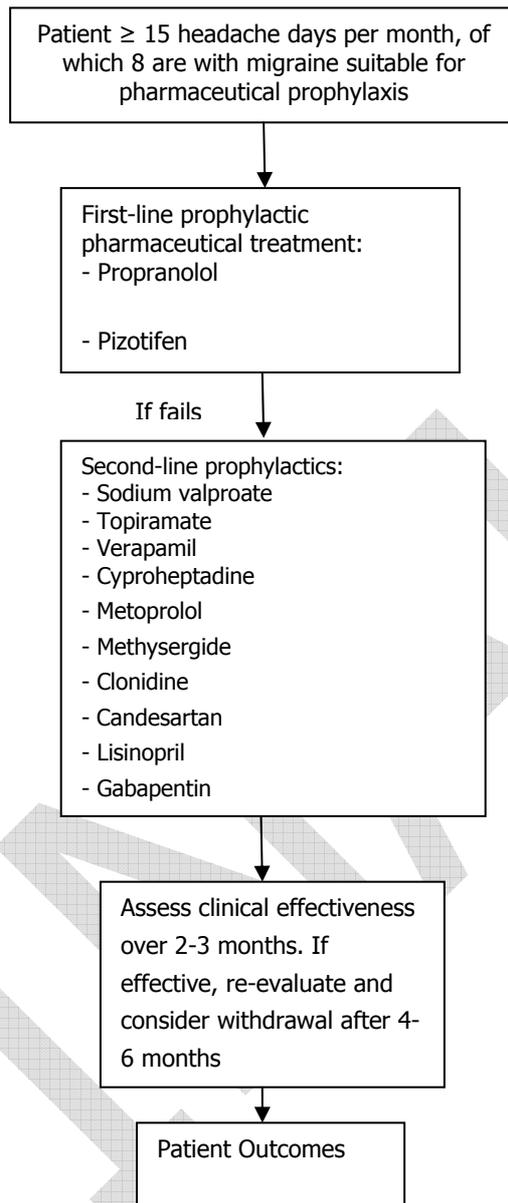
These guidelines, however, reflect only the *approved* uses of these pharmaceuticals. *In practice*, a number of other pharmaceuticals (some of which lack TGA approval and/or PBS reimbursement for migraine prophylaxis⁴) are also used for this purpose, as second-line options. They include:

- Cyproheptadine
- Metoprolol
- Methysergide
- Clonidine
- Candesartan
- Lisinopril
- Gabapentin (Stark and Stark, 2008).

A wide range of patient non-response to therapies is reported in published studies; clinical experts estimate that between 5-40% of patients do not respond to non-pharmaceutical therapies, pharmaceutical therapies, or both.

Current clinical management algorithm without the proposed intervention

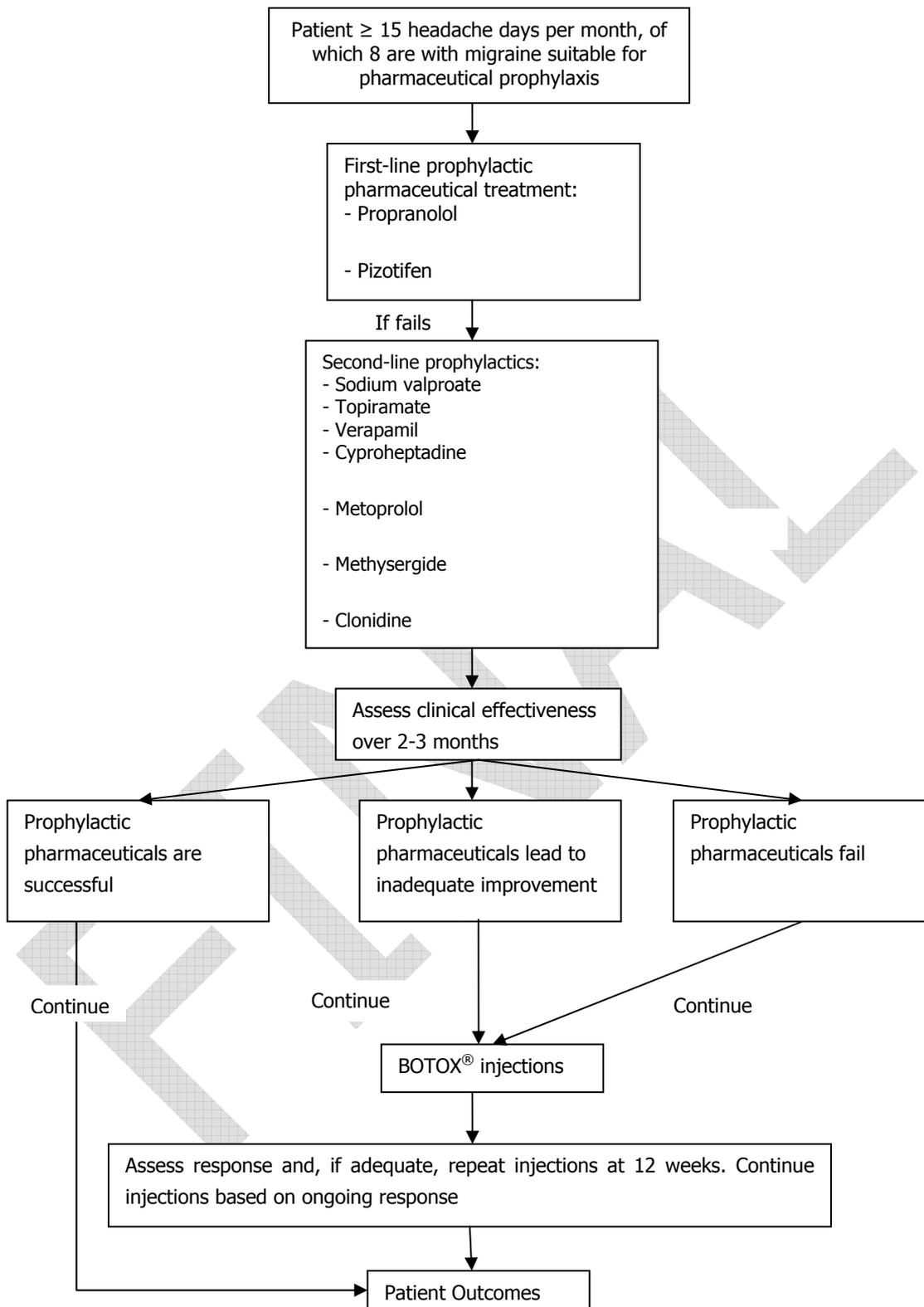
⁴ Their TGA and PBS status is indicated in Appendix 1.



Notes: this chart reflects *actual* (rather than approved) usage of pharmaceuticals. Concurrent medications for acute attacks (e.g. NSAIDS, triptans) are given throughout the time course of chronic migraine.

Current clinical management algorithm with the proposed intervention

As noted above, between 5-40% of patients fail to improve with conservative therapies. BOTOX® therapy is therefore proposed as a third-line option, as BOTOX® is more invasive than the first- and second-line conservative options.



Notes: this chart reflects *actual* (rather than approved) usage of pharmaceuticals. Concurrent medications for acute attacks (e.g. NSAIDS, triptans) are given throughout the time course of chronic migraine. Where prophylactic pharmaceuticals fail, they are normally continued; the decision to discontinue prophylaxis is more likely to occur after introducing the botulinum toxin than prior to its introduction.

Comparator

The comparator for patients who either fail or experience inadequate improvement with 1st and 2nd line prophylactics, is the best current practice, i.e. 1st and 2nd line prophylactic pharmaceuticals. PASC accepted that 'failure' and 'inadequate improvement' needs to be defined by PBAC.

Clinical claim

Because the application is a co-dependent technology (with *BOTOX*® to be assessed by PBAC and the *injection* of *BOTOX*® to be assessed by MSAC), Allergan has requested that the majority of the evaluative work (namely the comparative safety and effectiveness of the *BOTOX*® treatment, as well as the economic evaluation) be carried out by PBAC. Allergan has requested that MSAC's evaluation be circumscribed to the appropriate rebate for the injection procedure.

PASC agrees that the safety, effectiveness and cost effectiveness of *BOTOX*® should be assessed by PBAC, whilst the safety, effectiveness and cost-effectiveness of the delivery method (i.e., the injection) should be assessed by MSAC. However, as this is a co-dependent technology, the assessment of the delivery method will be modified by the assessment of the drug. Therefore, the data concerning *BOTOX*®'s safety and efficacy (which was presented to PBAC) will need to be considered by MSAC, as well.⁵

The safety issues to be considered here, include: bleeding, infection following treatment, safety of long-term repeat injections into the same location, pain from the injections, cosmetic side-effects from the injections (e.g. facial asymmetry from local muscle weakness near an injection site), generalised weakness, hyper-sensitivity (allergic) reaction, potentiation of anticholinergic effects (e.g., dryness of mouth and nose), headache (including worse migraine), myalgia, seizures; less frequently also a weakness remote from the injection site (e.g. neck weakness or impaired swallowing).

The effectiveness issues to be considered, include changes in: frequency of headache episodes, frequency of headache days, frequency of migraine episodes, frequency of migraine days, frequency of acute pain medication intake, frequency of prophylactic medication intake, change in number of moderate/severe headache days, changes in cumulative headache hours on headache days, changes in Headache Impact Test (HIT) score and percentage of patients with a severe HIT score.

As stated, the economic evaluation of the *BOTOX*® treatment would be carried out by PBAC and therefore Table 3 was not completed for this application. However, MSAC's assessment should consider the financial implications to the MBS of funding the new item (cost of the injection into the head and neck areas). Moreover, the projected user population for this indication (prophylaxis of migraine in chronic migraine patients) will need to be established, as well as the size of the

⁵ PBAC considered Allergan's application in its November 2011 meeting. The application was rejected on the basis of uncertain clinical benefit, and high and highly uncertain cost-effectiveness. Allergan intends to re-submit its application to PBAC.

population of episodic migraine patients and the potential for 'leakage' to that population should this item be placed on the MBS.

Table 3: Classification of an intervention for determination of economic evaluation to be presented

		Comparative effectiveness versus comparator									
		Superior		Non-inferior	Inferior						
Comparative safety versus comparator	Superior	CEA/CUA		CEA/CUA	<table border="1"> <tr> <td>Net clinical benefit</td> <td>CEA/CUA</td> </tr> <tr> <td>Neutral benefit</td> <td>CEA/CUA*</td> </tr> <tr> <td>Net harms</td> <td>None^</td> </tr> </table>	Net clinical benefit	CEA/CUA	Neutral benefit	CEA/CUA*	Net harms	None^
	Net clinical benefit	CEA/CUA									
	Neutral benefit	CEA/CUA*									
Net harms	None^										
Non-inferior	CEA/CUA		CEA/CUA*	None^							
Inferior	<table border="1"> <tr> <td>Net clinical benefit</td> <td>CEA/CUA</td> </tr> <tr> <td>Neutral benefit</td> <td>CEA/CUA*</td> </tr> <tr> <td>Net harms</td> <td>None^</td> </tr> </table>	Net clinical benefit	CEA/CUA	Neutral benefit	CEA/CUA*	Net harms	None^	None^		None^	
Net clinical benefit	CEA/CUA										
Neutral benefit	CEA/CUA*										
Net harms	None^										

Abbreviations: CEA = cost-effectiveness analysis; CUA = cost-utility analysis

* May be reduced to cost-minimisation analysis. Cost-minimisation analysis should only be presented when the proposed service has been indisputably demonstrated to be no worse than its main comparator(s) in terms of both effectiveness and safety, so the difference between the service and the appropriate comparator can be reduced to a comparison of costs. In most cases, there will be some uncertainty around such a conclusion (i.e., the conclusion is often not indisputable). Therefore, when an assessment concludes that an intervention was no worse than a comparator, an assessment of the uncertainty around this conclusion should be provided by presentation of cost-effectiveness and/or cost-utility analyses.

^ No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this intervention

Outcomes and health care resources affected by introduction of proposed intervention

Outcomes

This assessment will consider:

- Safety of the injection of BOTOX® into the head and neck areas
 - Bleeding
 - Infection following treatment
 - Safety of long-term repeat injections into the same location
 - Pain from the injections
 - Cosmetic side-effects from the injections (e.g. facial asymmetry from local muscle weakness near an injection site)
 - generalised weakness

- hyper-sensitivity (allergic) reaction
- potentiation of anticholinergic effects
- headache (including worse migraine)
- myalgia
- seizures
- weakness remote from the injection site (e.g. neck weakness or impaired swallowing)
- Effectiveness of the injection (as modified by evidence of the effectiveness of BOTOX®)
 - Frequency of headache episodes
 - Frequency of headache days
 - Frequency of migraine episodes
 - Frequency of migraine days
 - Frequency of acute pain medication intake
 - Frequency of prophylactic medication intake
 - Change in the number of moderate/severe headache days
 - Changes in cumulative headache hours on headache days
 - Changes in Headache Impact Test (HIT) score
 - Percentage of patients with a severe HIT score
- Cost-effectiveness:
 - Cost of injection of BOTOX® into the head and neck areas
 - Size of the chronic migraine patient population
 - Size of the episodic migraine patient population (and potential for 'leakage')

Health care resources

Table 4: List of resources to be considered in the economic analysis

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other govt budget	Private health insurer	Patient	Total cost
<u>Resources provided to identify eligible population</u>										
- Resource 1										
- Resource 2, etc										
<u>Resources provided to deliver comparator 1</u>										
- Resource 1										
- Resource 2, etc										
<u>Resources provided in association with comparator 1 (e.g., pre-treatments, co-administered interventions, resources used to monitor or in follow-up, resources used in management of adverse events, resources used for treatment of downstream conditions): Current best practice</u>										
- Resource 1	Neurologist consult	Outpatient								
- Resource 2, etc										
<u>Resources provided to deliver comparator 2, etc</u>										
- Resource 1										
- Resource 2, etc										
<u>Resources provided in association with comparator 2, etc</u>										
- Resource 1										
- Resource 2, etc										
<u>Resources provided to deliver proposed intervention</u>										
- Resource 1										
- Resource 2, etc										
<u>Resources provided in association with proposed intervention</u>										
- Resource 1										
- Resource 2, etc										

Proposed structure of economic evaluation (decision-analytic)

Table 5: Summary of extended PICO to define research question that assessment will investigate

Patients	Intervention	Comparator	Outcomes to be assessed	Healthcare resources to be considered
<p>Patients \geq 15 headache days per month, of which 8 are with migraine, who either fail or experience inadequate improvement with 1st and 2nd line prophylactics</p>	<p>Injection of BOTOX® into head and neck areas</p>	<p>Best current practice, i.e. 1st and 2nd line prophylactic pharmaceuticals</p>	<p>Safety:</p> <ul style="list-style-type: none"> • Bleeding • Infection following treatment • Safety of long-term repeat injections into the same location • Pain from the injections • Cosmetic side-effects • Generalised weakness • Hyper-sensitivity (allergic) reaction • Anticholinergic effects • Headache • Myalgia • Seizures • Weakness remote from the injection site <p>Effectiveness:</p> <ul style="list-style-type: none"> • Freq. of headache episodes • Freq. of headache days • Freq. of migraine episodes • Freq. of migraine days • Freq. of acute pain medication intake • Freq. of prophylactic medication intake • Change in no. of moderate/severe headache days • Change in cumulative headache hrs on headache days • Changes in HIT score • % of patients with severe HIT score 	<p>Cost of the injection of BOTOX® into head and neck areas</p> <p>Size of the chronic migraine patient population</p> <p>Size of the episodic migraine patient population and the potential for 'leakage'</p>

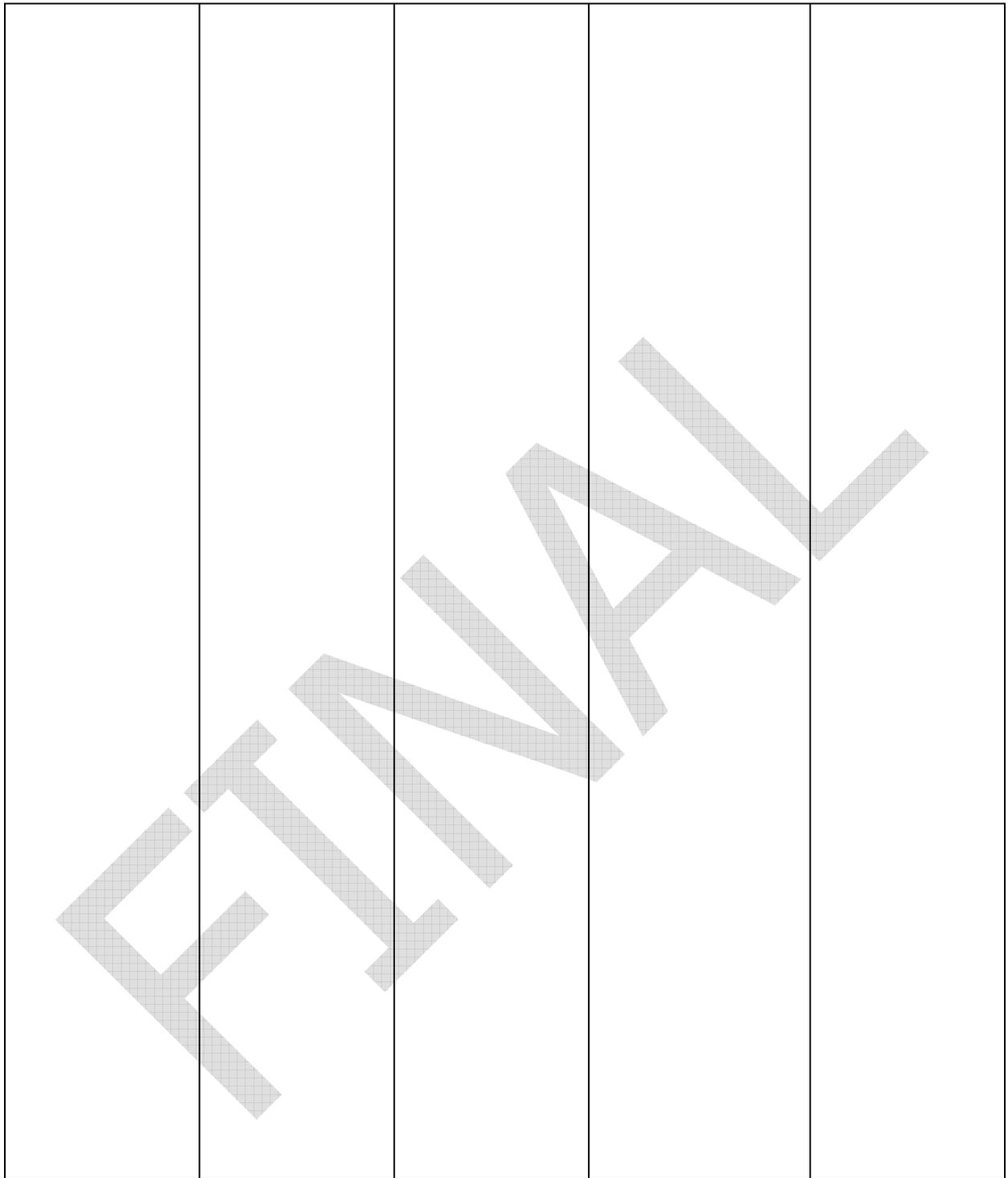
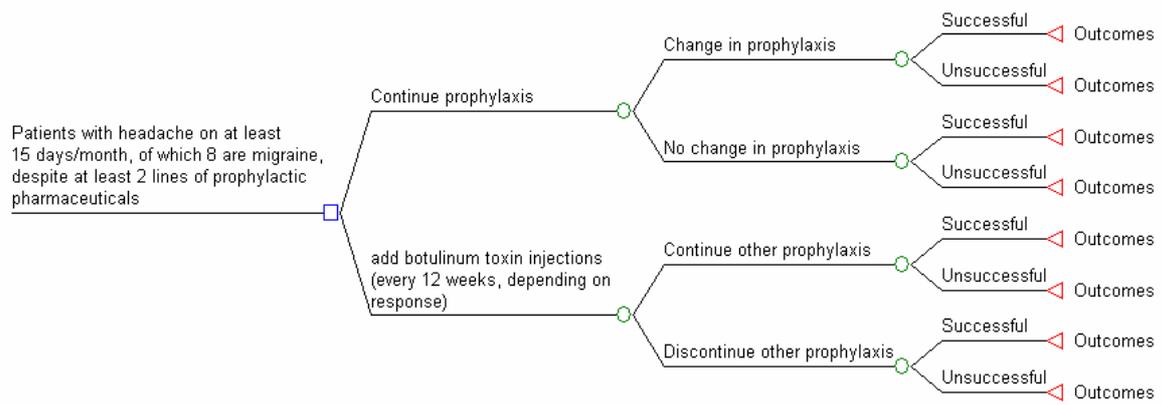


Figure 1: Decision Analytic Tree



FEMVA

Appendix 1: TGA and PBAC status of other pharmaceuticals used for prophylaxis of migraine.

Drug	TGA status	PBS status
Cyproheptadine	Migraine	Restricted benefit – prevention of migraine
Metoprolol	Prevention of migraine	General benefit
Methysergide	Prophylaxis of migraine	General benefit
Clonidine	Prophylaxis of migraine	General benefit
Candesartan	Not registered for migraine	General benefit (cardiovascular)
Lisinopril	Not registered for migraine	General benefit (cardiovascular)
Gabapentin	Not registered for migraine	Authority required (streamlined)

(Stark and Stark, 2008; PBS online <http://www.pbs.gov.au/pbs/home> accessed January 6th, 2012)

Appendix 2: Botox uses currently reimbursed by MBS

MBS 18350

BOTULINUM TOXIN (Botox), injection of, for hemifacial spasm in a patient 12 years of age or older, including all injections on any one day

(See para T11.1 of explanatory notes to this Category)

Fee: \$120.10

MBS 18352

BOTULINUM TOXIN (Botox or Dysport), injection of, for cervical dystonia (spasmodic torticollis), including all injections on any one day

(See para T11.1 of explanatory notes to this Category)

Fee: \$240.30

MBS 18354

BOTULINUM TOXIN (Botox or Dysport), injection of, for dynamic equinus foot deformity due to spasticity in an ambulant cerebral palsy patient, aged two years or older, in accordance with the 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*, including all such injections on any one day for all or any of the muscles subserving one functional activity and supplied by one motor nerve - applicable only to the first two treatments of each limb of the patient on any one day

(See para T11.1 of explanatory notes to this Category)

Fee: \$120.10

MBS 18356

BOTULINUM TOXIN (Botox or Dysport), injection of, for dynamic equinovarus foot deformity due to spasticity in an ambulant cerebral palsy patient, aged two years or older, in accordance with the 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*, including all such injections on any one day for all or any of the muscles subserving one functional activity and supplied by one motor nerve - applicable only to the first two treatments of each limb of the patient on any one day

(Anaes.)

(See para T11.1 of explanatory notes to this Category)

Fee: \$120.10

MBS 18358

BOTULINUM TOXIN (Botox or Dysport), injection of, for dynamic equinovalgus foot deformity due to spasticity in an ambulant cerebral palsy patient, aged two years or older, in accordance with the 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*, including all such injections on any one day for all or any of the muscles subserving one functional activity and supplied by one motor nerve - applicable only to the first two treatments of each limb of the patient on any one day

(Anaes.)

(See para T11.1 of explanatory notes to this Category)

Fee: \$120.10

MBS 18360

BOTULINUM TOXIN (Botox), injection of, for the treatment of focal spasticity in adults, including all injections for all or any of the muscles subserving one functional activity, supplied by one motor nerve, with a maximum of 4 treatments per patient on any one day (2 per limb)

(See para T11.1 of explanatory notes to this Category)

Fee: \$120.10

MBS 18361

Botulinum toxin (Botox), injection of, for the treatment of moderate to severe upper limb spasticity due to cerebral palsy, in a patient who is at least 2 years but less than 18 years, in association with either: (a) physiotherapy or occupational therapy or both; or (b) electrical stimulation or ultrasound for muscle localisation; including all injections for any or all of the muscles sub-serving one functional activity supplied by one motor nerve - with a maximum of four treatments per patient on any one day, and with a maximum of two treatments

per limb

(Anaes.)

(See para T11.1 of explanatory notes to this Category)

Fee: \$120.10

MBS 18362

BOTULINUM TOXIN (Botox), injection of, for the treatment of severe primary hyperhidrosis of the axillae, including all such injections on any one day

(See para T11.1 of explanatory notes to this Category)

Fee: \$237.35

MBS 18366

BOTULINUM TOXIN (Botox), injection of, for the treatment of strabismus in children and adults, including all such injections on any one day and associated electromyography

(See para T11.1 of explanatory notes to this Category)

Fee: \$150.50

MBS 18368

BOTULINUM TOXIN (Botox), injection of, for the treatment of spasmodic dysphonia, including all such injections on any one day

(See para T11.1 of explanatory notes to this Category)

Fee: \$256.90

MBS 18370

BOTULINUM TOXIN (Botox), injection of, for the treatment of blepharospasm in a patient 12 years of age or older, including all such injections on any one day.

(See para T11.1 of explanatory notes to this Category)

Fee: \$43.35

MBS 18372

BOTULINUM TOXIN (Botox), injection of, for the treatment of bilateral blepharospasm in a patient 12 years of age or older, including all such injections on any one day

(See para T11.1 of explanatory notes to this Category)

Fee: \$120.10

T.11.1. BOTULINUM TOXIN - (ITEMS 18350 TO 18373)

The Therapeutic Goods Administration (TGA) assesses each indication for the therapeutic use of botulinum toxin on an individual basis. There are currently two botulinum toxin agents with TGA registration (Botox and Dysport). Each has undergone a separate evaluation of its safety and efficacy by the TGA as they are neither bioequivalent, nor dose equivalent. When claiming under an item for the injection of botulinum toxin, only the botulinum toxin agent specified in the item can be used. Benefits are not payable where an agent other than that specified in the item is used.

The TGA assesses each indication for the therapeutic use of botulinum toxin by assessment of clinical evidence for its use in paediatric or adult patients. Where an indication has been assessed for adult use, data has generally been assessed using patients over 12 years of age. Paediatric indications have been assessed using data from patients under 18 years of age. Botulinum toxin should only be administered to patients under the age of 18 where an item is for a paediatric indication, and patients over 12 years of age where the item is for an adult indication, unless otherwise specified.

Items for the administration of botulinum toxin can only be claimed by a medical practitioner who is registered by Medicare Australia to participate in the arrangements under Section 100 of the *National Health Act 1953* relating to the use and supply of Botulinum Toxin.

Items 18354, 18356 and 18358 for the treatment of equinus, equinovarus or equinovalgus are limited to a maximum of 4 injections per patient on any one day (2 per limb). Accounts should be annotated with the limb which has been treated.

Item 18292 may not be claimed for the injection of botulinum toxin, but may be claimed where a neurolytic agent (such as phenol) is used, in addition to botulinum toxin injection(s), to treat the obturator nerve in patients with a dynamic foot deformity.

Items 18354 to 18358 have been extended to patients 18 years of age and older who have commenced on the PBS subsidised treatment as a paediatric patient. This is in line with the extension of the PBS listing for the supply of the drug for this indication under Section 100(1)(b) of the *National Health Act 1953*.

Botulinum Toxin, which is not supplied and administered in accordance with the arrangements under Section 100 of the *National Health Act 1953*, is not free of charge to patients. Where a charge is made for the Botulinum Toxin administered, it must be separately listed on the account and not billed to Medicare.

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