Botulinum toxin type A for chronic migraine: 24 month predicted versus actual analysis

Drug utilisation sub-committee (DUSC)

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Abstract

Purpose

To compare the predicted and actual utilisation of botulinum toxin type A (Botox®) for chronic migraine in adults since it was PBS listed for this indication in March 2014.

Current PBS restriction for chronic migraine

Authority required (Streamlined)

Patients must have experienced an average of 15 or more headache days per month, with at least 8 days of migraine, over a period of at least 6 months, prior to commencement of treatment with botulinum toxin type A neurotoxin, AND;

Patients must have experienced an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications prior to commencement of treatment with botulinum toxin type A neurotoxin (prophylactic migraine medications are propranolol, amitriptyline, methysergide, pizotifen, cyproheptadine or topiramate) AND;

Patients must be appropriately managed by his or her practitioner for medication overuse headache, prior to initiation of treatment with botulinum toxin AND;

Patients must be aged 18 years or older and must be treated by a neurologist.

Patients must have achieved and maintained a 50% or greater reduction from baseline in the number of headache days per month after two treatment cycles (each of 12 weeks duration) in order to be eligible for continuing PBS-subsidised treatment.

Botox® is the only botulinum toxin type A preparation PBS subsidised for chronic migraine. For brevity the term 'botulinum toxin' is used throughout this report.

Data Sources

Data to assess utilisation of botulinum toxin for chronic migraine was obtained from three sources:

- Department of Human Services (DHS) - Complex Drugs (Tasmania) Section 100 Botulinum Toxin Program reports
- DHS Pharmaceutical Benefits Scheme (PBS) prescription claims data
- DHS Medicare Benefits Schedule (MBS) claims data relating to injection services for botulinum toxin A (Item 18377 for chronic migraine).

Key Findings

- There were 3,517 and 5,444 patients treated with botulinum toxin for chronic migraine in the first and second year of PBS listing, respectively. The number of patients treated was substantially higher than predicted.
- There were 7,826 and 13,873 services for the administration of botulinum toxin in the first and second year of listing, respectively, substantially more than expected.
- Continuation rate on treatment at 24 weeks (i.e. after 2 treatments), 71.4%, was more than double that predicted from trial data, 32.9%.
- PBS prescription data are insufficient to assess compliance with the PBS restriction regarding patients having experienced an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications and management of medication overuse headache prior to commencing botulinum toxin. Many prophylactic and acute treatments for migraine are available over the counter, can be provided on private prescription, and/or are priced under the general patient co-payment and are not included in the PBS dataset.
- Treatment rates in most states were similar with approximately 23-32 patients per 100,000. Treatment rates were substantially higher in the ACT (105 per 100,000) and substantially lower in the NT (5 per 100,000).

Purpose of analysis

To compare the predicted and actual utilisation of botulinum toxin type A (Botox®) for chronic migraine in adults since it was listed for this indication in March 2014.

Background

Clinical situation

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) .The International Classification for Headache Disorders defines chronic migraine as headache on at least 15 days per month, with at least 8 headache days meeting the criteria for migraine without aura.[1]

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

Pharmacology[2]

Botulinum toxin type A is a neuromuscular blocking agent that blocks peripheral acetylcholine release at presynaptic cholinergic nerve terminals by cleaving SNAP-25, a protein integral to the docking and release of acetylcholine from vesicles located within the nerve terminals.

Limited nonclinical data suggest that Botox® may reduce sensitisation processes, but the actual mechanism of action for headache prophylaxis is not known.

Therapeutic Goods Administration (TGA) approved indications[2]

Botox® was registered by the TGA on 5 March 2011 for the indication:

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

[1] International Classification of Headache Disorders, Second Edition, Revised. Source: Olesen et al. 2006. *There have been no changes to the definition of chronic migraine in the subsequent edition (ICHD-3 beta).*

[2] Botox (botulinum toxin type A) Australian Approved Product Information. Allergan Australia Pty Ltd. Date of most recent amendment: 24 September 2015. Available from <https://www.ebs.tga.gov.au/>. Accessed 24 April 2017

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

- treatment of overactive bladder with symptoms of urinary incontinence, urgency and frequency, in adult patients who have an inadequate response to or are intolerant of an anticholinergic medication
- treatment of urinary incontinence due to neurogenic detrusor overactivity resulting from a defined neurological illness (such as spinal cord injury or multiple sclerosis) and not controlled adequately by anticholinergic agents
- treatment of strabismus in children and adults
- treatment of blepharospasm associated with dystonia, including benign blepharospasm and VIIth 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 and older
- treatment of severe primary hyperhidrosis of the axillae
- treatment of focal spasticity in adults
- treatment of spasmodic dysphonia.

Many of these indications are PBS subsidised under certain circumstances for patients meeting defined criteria. Refer to pbs.gov.au for full details.

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

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

Dosage and administration[3]

A brief summary of the dosage and administration for Botox® for the chronic migraine indication is provided below. Refer to the Product Information (PI) for full details available from the TGA website.

Botox should only be given by physicians with the appropriate qualifications and experience in the treatment of patients and the use of required equipment.

The recommended dose for treating chronic migraine is 155 U to 195 U administered intramuscularly (IM) . Injections should be divided across 7 specific head/neck muscle areas as specified in the Product Information. A summary is provided in Appendix A. The recommended re-treatment schedule is every 12 weeks.

Due to the difficulties in establishing a diagnosis of chronic migraine, patients being considered for prophylaxis of headaches with Botox should be evaluated by a neurologist or pain management specialist prior to receiving treatment with Botox. The use of Botox for prophylaxis of headaches in adults with chronic migraine has been assessed for 3 cycles

[3] Botox (botulinum toxin type A) Australian Approved Product Information. Allergan Australia Pty Ltd. Date of most recent amendment: 24 September 2015. Available from <https://www.ebs.tga.gov.au/>. Accessed 24 April 2017

over 32 weeks. No long term safety or efficacy data for this indication are available. Patients who do not have an adequate response after 2 treatment cycles should not continue treatment. Patients should not receive more than 3 cycles of treatment prior to an assessment of the need for further treatment.

The TGA approved PI for Botox states that due to the lack of an international unit Botox is not therapeutically equivalent to any other botulinum toxin preparations.

Relevant aspects of consideration by the PBAC (abridged)

At its July 2013 meeting the Pharmaceutical Benefits Advisory Committee (PBAC) recommended Section 100 Botulinum Toxin Program listing for botulinum toxin type A for prophylaxis of headaches in adult patients with chronic migraine who meet certain criteria, on the basis of acceptable cost-effectiveness compared to best supportive care.

The PBAC had considered two previous submissions (November 2011 and July 2012) requesting this extension to listing. The PBAC rejected the November 2011 submission on the basis of uncertain clinical benefit and highly uncertain cost effectiveness. The PBAC rejected the July 2012 re-submission on the basis of uncertain cost effectiveness.

The PBAC considered that a clinical need exists for an effective treatment for refractory chronic migraine, unresponsive to multiple oral prophylactic medications. The PBAC accepted that best supportive care was the appropriate comparator for patients who have failed at least three lines of therapy.

In recommending listing, the PBAC considered the base case ICER ( ) was acceptable, but may not represent the true cost effectiveness in clinical practice given a number of issues with the economic evaluation including the transition probabilities, the utility values, the extrapolation of the incremental treatment effect of botulinum toxin beyond the trial duration to 5 years in the absence of supportive evidence, the assumption of perfect compliance to the continuation rule in the requested restriction, and the use of the commissioned Burden of Illness study as the source of the utility values and resource utilisation costs in the economic model.

The PBAC noted that the re-submissions' estimates of patients treated, prescriptions and packs dispensed, and net costs to the PBS/MBS were higher than in previous submissions ( ). The PBAC considered the estimates to be uncertain due to the reasons identified by the DUSC in November 2011. The DUSC had advised 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 had also considered there was considerable risk of usage beyond the restriction in partial responders, although acknowledged that the invasive nature of botulinum toxin administration may serve to limit use in partial and non-responders.

To manage uncertainty in the financial estimates and to address concerns with potential usage beyond the restriction the Sponsor proposed a risk sharing arrangement with two subsidisation caps (RSA). [redacted]

Given the PBAC's concern about the likelihood of the estimated ICER being reflected in practice, the expected difficulty in differentiating use within and beyond the intent of the restriction, and the uncertainty in the estimated PBS usage and financial implications, the Committee recommended that a tighter RSA be negotiated with the Sponsor and that the caps be based on the smaller estimates of use provided in the July 2012 resubmission.

Listing was effective from 1 March 2014.

For further details refer to the Public Summary Document by product or meeting.

Approach taken to estimate utilisation

Table 1 shows the assumptions and data sources used to estimate utilisation in the original submission and the two resubmissions.

Table 1: Summary of assumptions and data sources used in submissions

Variable	First submission (November 2011 PBAC)	1st Resubmission (July 2012 PBAC)	2nd Resubmission (July 2013 PBAC)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

PBS listing details (as at April 2017)

Table 3: PBS listing of botulinum toxin type A for chronic migraine

Item	Name, form & strength, pack size	Max qty packs	Rpts	DPMQ	Brand name and manufacturer
6103F 11000Y[#]	botulinum toxin type A 100 units injection, 1 vial	4	0	1625.94*	Botox, Allergan Australia Pty Limited

Source: pbs.gov.au

[#] New PBS item code from 1 January 2017

*Special Pricing Arrangements apply

Note: Streamlined Authority code for the Chronic Migraine indication is 5262

Restriction

Authority required (Streamlined)

Patient must have experienced an average of 15 or more headache days per month, with at least 8 days of migraine, over a period of at least 6 months, prior to commencement of treatment with botulinum toxin type A neurotoxin, AND;

Patient must have experienced an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications prior to commencement of treatment with botulinum toxin type A neurotoxin. Prophylactic migraine medications are propranolol, amitriptyline, methysergide, pizotifen, cyproheptadine or topiramate AND;

Patient must be appropriately managed by his or her practitioner for medication overuse headache, prior to initiation of treatment with botulinum toxin AND;

Patients must be aged 18 years or older and must be treated by a neurologist.

Patient must have achieved and maintained a 50% or greater reduction from baseline in the number of headache days per month after two treatment cycles (each of 12 weeks duration) in order to be eligible for continuing PBS-subsidised treatment.

For full details of the current PBS-listing refer to the PBS website.

Changes to listing and supply arrangements

In recent years there have been two reforms to the way PBS subsidised botulinum toxin is supplied. The intent of the PBS restriction, including patient and prescriber eligibility criteria, has remained unchanged.

Prior to 1 September 2015 botulinum toxin was available via the *National Health (Botulinum toxin Program) Special Arrangement 2011*. This program provided alternative arrangements for distribution of botulinum toxin. Prescribers were required to be individually authorised to prescribe botulinum toxin under the PBS following application to the Department of Human Services (DHS). Prescribers then telephoned DHS to arrange direct supply of the drug to the prescriber by the pharmaceutical company.

From 1 September 2015 the way PBS-subsidised botulinum toxin was supplied changed to better align with other PBS arrangements, using PBS prescriptions and hospital pharmacy coordination points. The revised arrangements were supported through the *National Health (Botulinum Toxin Program) Special Arrangement 2015.* This change meant that eligible PBS botulinum toxin prescriptions are now claimed like other PBS prescriptions and prescription level data is made available to the Department of Health for analysis. This change required adaption of the Program from manual ordering by clinics through DHS to a system of Streamlined Authority prescriptions.

From 1 July 2015, in preparation for the above change and following endorsement by the PBAC, the restriction text for this indication was updated as follows;

- to specify treatment by neurologists. Previously this requirement was effected through Section 17A of the *National Health (Botulinum Toxin Program) Special Arrangement 2011* under the *National Health Act 1953*;
- replace 'patient must be an adult' with 'patient must be aged 18 years or older' clarifying the definition of an adult;
- to explicitly list the prophylactic medicines that patients are required to have failed at least three of, or be contraindicated or intolerant of, prior to using botulinum toxin (propranolol, amitriptyline, methysergide, pizotifen, cyproheptadine or topiramate); and
- to specify maximum quantity of 4 vials with zero repeats.

The implementation of the Authority required (STREAMLINED) restriction meant that prescribers were no longer required to telephone DHS for authorisation and ordering supply. Prescribers must write a prescription for each patient ensuring the prescriptions they write comply with PBS requirements for subsidised botulinum toxin, including patient and prescriber eligibility criteria. As direct patient handing of botulinum toxin is not permitted, hospital pharmacies co-ordinate the supply to physicians.

Changes to the *National Health (Botulinum Toxin Program) Special Arrangement 2015* (effective 1 March 2017) allows prescribers to write two prescriptions for botulinum toxin on the same day, where a patient requires treatment for two different indications. Due to the limitation of the DHS PBS Online system, changes in the PBS item codes were required. From 1 January 2017 the number of PBS item codes for botulinum toxin type A increased from one (6103F), where the indication was specified by using different Streamlined Authority codes, to eight, where there is one PBS item number (and Streamlined Authority code) for each indication.

Further information and frequently asked questions regarding the 1 September 2015 and 1 January 2017 – 1 March 2017 changes are available from the PBS website.

MBS listing details **(as at February 2017)**

The MBS service associated with the administration of PBS subsidised botulinum toxin for chronic migraine is as follows:

MBS Item 18377

Botulinum Toxin Type A Purified Neurotoxin Complex (Botox), injection of, for the treatment of chronic migraine, including all injections in 1 day, if:
(a) the patient is at least 18 years of age; and
(b) the patient has experienced an inadequate response, intolerance or contraindication to at least 3 prophylactic migraine medications before commencement of treatment with botulinum toxin, as manifested by an average of 15 or more headache days per month, with at least 8 days of migraine, over a period of at least 6 months, before commencement of treatment with botulinum toxin; and
(c) the requirements relating to botulinum toxin type A under the Pharmaceutical Benefits Scheme are complied with.

For each patient, applicable not more than twice except if the patient achieves and maintains at least a 50% reduction in the number of headache days per month from baseline after 2 treatment cycles (each of 12 weeks duration)

Fee: $124.85 **Benefit:** 75% = $93.65 85% = $106.15

Further information is available from the MBS online website.

Methods

Multiple data sources were required to assess the utilisation of botulinum toxin because only aggregate PBS data was available prior to the transition to prescription based supply. This was recognised by DUSC at its June 2016 meeting when the committee decided to delay the 24 month predicted versus actual analysis for chronic migraine until there was at least a full year of prescription data available.

DUSC had also suggested that analysis of other migraine therapies (at a patient level) would provide insight into whether use is for chronic migraine. DUSC also considered that analysis by state and linkage with MBS data may be informative in understanding patterns of use.

Data Sources

Three sources of data were used:

- DHS - Complex Drugs (Tasmania) Section 100 Botulinum Toxin Program reports
- DHS - PBS prescription claims data
- DHS - MBS services data for administration of PBS subsidised botulinum toxin.

Section 100 Botulinum Toxin Program Reports

The reports from DHS Complex Drugs (Tasmania) for the Section 100 Botulinum Toxin Program provide aggregate data on the number of treatments and vials approved for supply and a cumulative count of patients approved for the indication. Reports were available for the period 1 March 2014 to 31 January 2016. The program became prescription based in September 2015, however there were transitional arrangements available until 31 December 2015 with claims being accepted up until January 2016 for claims not finalised via the previous mechanism. The reports use the terminology 'treatments' which is equivalent to one prescription.

Data from these reports were used to determine the number of treatments and the mean number of vials per treatment supplied under the old Special Arrangement.

PBS prescription claim data

PBS prescription data for botulinum toxin from 1 September 2015 to 31 December 2016 were extracted from the DHS prescription database based on the date of dispensing. The date of dispensing may differ from the date of administration because prescribers may order botulinum toxin medicines from hospital pharmacies in advance of providing a valid PBS prescription/s to cover the supply. PBS Regulations require prescribers to make prescriptions available within seven days of a verbal or written order[4]. The date of processing of the PBS prescription may also differ from the date of dispensing. Consequently there may be differences in data reported by date of dispensing or processing (such as that available publicly available from DHS Medicare website).

[4] http://www.pbs.gov.au/general/changes-to-certain-s100-programs/botulinum-toxin-program-frequently-asked-questions.pdf

PBS prescription data were used to determine the number of prescriptions supplied, the number of vials supplied and the number of vials per prescription for botulinum toxin for chronic migraine. The data were also used to count the number of neurologists who prescribed botulinum toxin for chronic migraine and the number of neurologists who prescribed any PBS medicine in 2016 where there was complete data capture.

MBS services data

MBS item level services data based on date of service for all item codes in MBS Group T11 (Botulinum Toxin Injections) from 1 March 2014 to the most recent reasonably complete month, November 2016, was provided by the MBS Analytics Section, Primary Care and Diagnostics Branch, Medicare Benefits Division, Commonwealth Department of Health. The MBS item associated with administration of botulinum toxin to patients with chronic migraine who meet the PBS criteria is 18377. As the MBS data is based on date of service, recent service volumes could be marginally incomplete and may continue to change over time as additional claims are submitted. The date of service data contains date of processing to 6/3/2017.

MBS services data were used as an alternative data source for assessing utilisation of botulinum toxin where this was not possible from the PBS data. A difference between the PBS and MBS data is that MBS data does not include repatriation patients and will therefore underestimate the utilisation of botulinum toxin supplied through the PBS for this group of patients. The impact of this is small because PBS data (which includes Repatriation PBS (RPBS) prescriptions) show that 0.39% of all PBS prescriptions in the period 1 September 2015 to 31 December 2016 were RPBS.

The MBS data were used to count the number of incident and prevalent patients receiving treatment and to determine rates of treatment continuation. Initiation was defined as a patient's first service for MBS item 18377. A comparison of treatment rates across States was based on the patient's Medicare enrolment address at the time the service was processed by DHS.

Data linkage

Linkage of MBS and PBS data was achieved by matching the Patient ID field that was present in both the PBS and MBS datasets. Specific permission was given as required under Guidelines from the Privacy Commission under section 135AA of The National Health Act 1953 to enable this data matching and all records were destroyed after the analysis as required by the Privacy Commissioner's Guidelines. All patients IDs are de-identified.

The linked data was used to assess how many prophylactic migraine medicines patients had used prior to commencing botulinum toxin. Commencement of treatment with botulinum was determined by their first MBS service for injection rather than from the PBS data because of the limitations of the Botulinum Program data described above.

The cohort analysed for prior prophylactic migraine medicines initiated botulinum toxin from 1 April to 30 November 2016. Earlier initiators were not included to maximise the

length of PBS prescription history after the inclusion of general patient undercopayment prescriptions in the PBS data in April 2012.

After establishing a patient's initiation date using MBS data, all PBS prescription data for the patients in this cohort were extracted from the DHS prescription database from January 2003 to the end of December 2016 (based on the date of dispensing).

Thus there was at least a 4 year lookback period for each patient across PBS data with complete capture (i.e. including general patient undercopayment prescriptions) and then a further lookback from March 2012 to January 2003 where there was incomplete capture for PBS items priced under the general copayment (i.e. not captured for general patients). The implications of this period of incomplete data is discussed in the results section.

Results

Utilisation

Figure 1 shows the utilisation of botulinum toxin for chronic migraine is increasing and is yet to stabilise.

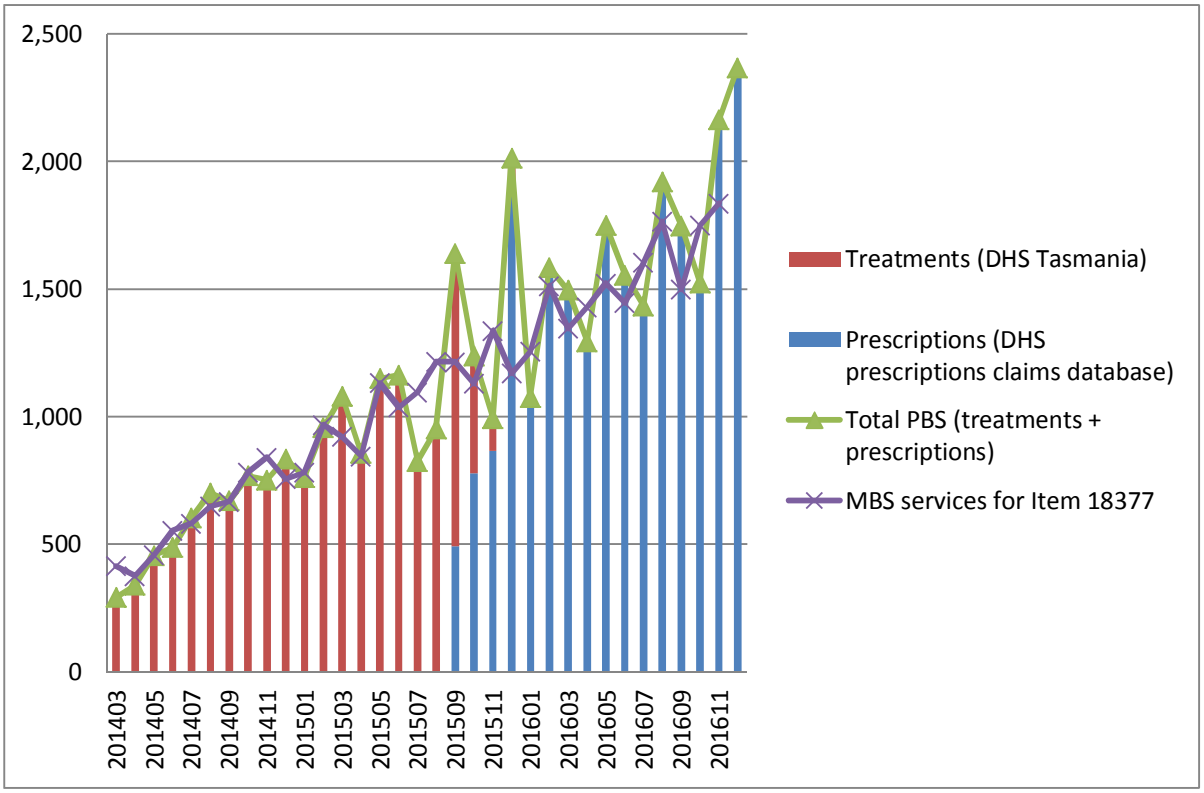

Figure 1: Treatments / prescriptions of botulinum toxin and MBS services for injection for chronic migraine Sources: treatments sourced from DHS - Complex Drugs (Tasmania). Prescriptions (by date of supply) sourced from DHS prescription claims database (accessed 21 March 2017). MBS services sourced from claims data (MBS Item 18377 for injection of botulinum toxin for chronic migraine).

The red bars represent the number of treatments approved through the Botulinum Toxin Program in the period before and during the transition to prescription based supply. The blue bars represent the number of prescriptions dispensed following introduction of prescription based supply. Some supply continued via the previous program mechanism for several months after prescription supply commenced. This arrangement was phased out in January 2016. There was some volatility in utilisation around the time of the introduction of the prescription base system. This may be due to a backlog of claims being submitted and processed and/or because PBS botulinum toxin supplies accumulated by prescribers under the arrangements in effect prior to 1 September 2015 could be used at prescribers' discretion, provided that they are administered to patients who meet the eligibility requirements for PBS subsidy.

The utilisation of services through the MBS for the administration of botulinum toxin (purple line) align with the PBS utilisation. MBS services therefore represents a useful alternative source of data on the utilisation of PBS subsidised botulinum toxin for chronic

migraine and offers the advantage of complete patient level data throughout the listing period. It should be noted that the MBS data does not contain services for Department of Veterans Affairs (DVA) cardholders, whereas the PBS data does contain treatments and prescriptions (Repatriation PBS, RPBS) for these patients. The percentage of total prescriptions from September 2015 to the end of December 2016 that were RPBS was 0.39%. This will make a negligible difference when comparing PBS prescriptions and MBS services and patient counts base on MBS or PBS.

The MBS data was used to count the number of patients (initiating and prevalent) receiving treatment with botulinum toxin for chronic migraine (Figure 2).

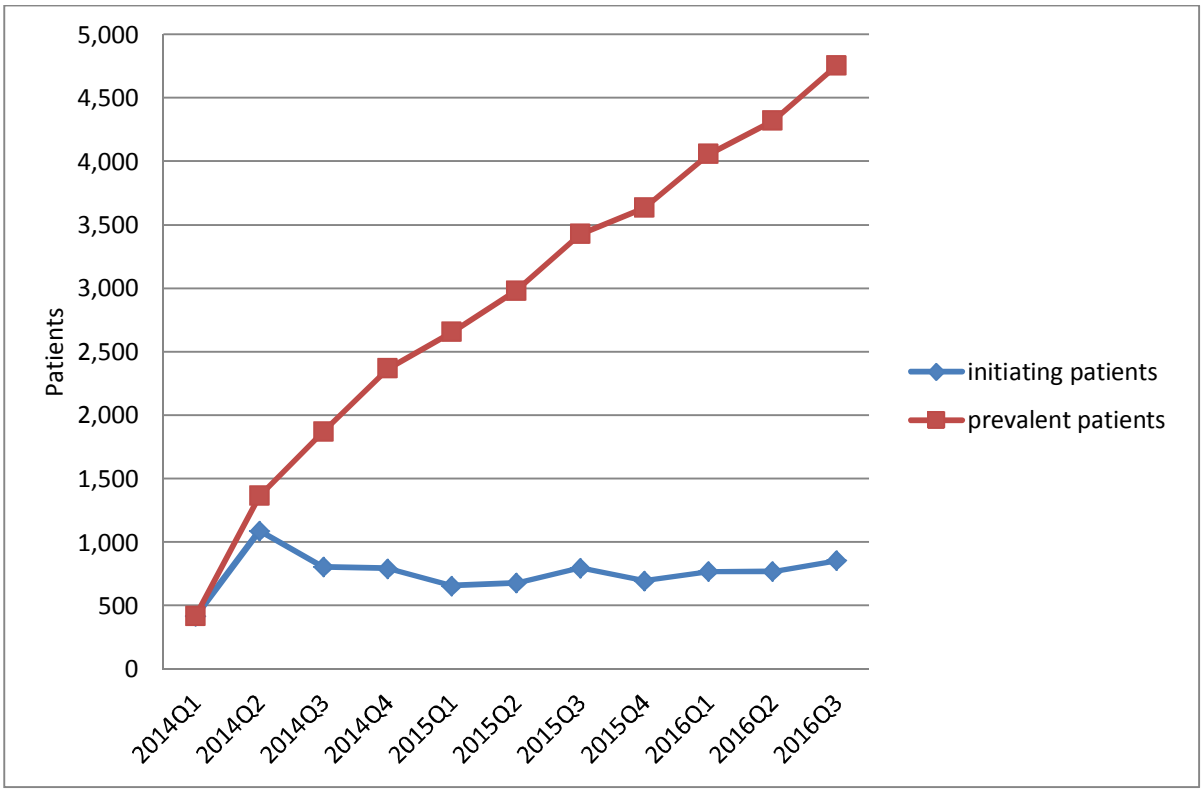

Figure 2: Number of patients initiating and prevalent to MBS Item 18377 (MBS service for injection of Botox for chronic migraine)

The number of patients receiving their first MBS service for administration of botulinum toxin for chronic migraine (initiating patients) peaked soon after listing, likely due to unmet need in patients who had failed other prophylactic medicines and patients who were paying for botulinum toxin privately moving to PBS supply. The number of new patients has since been comparatively stable. Further data will be required to determine if the slight increase in the number of new patients in the third quarter of 2016 is sustained. The fourth quarter of 2016 is not shown as MBS data was only complete until the end of November 2016.

The number of prevalent patients has increased strongly suggesting that many patients are continuing on therapy. This is investigated further later in this report. It is worthwhile noting that the number of prevalent patients treated in a quarter is likely to underestimate

treated prevalence for a drug administered in 12 week cycles as time between treatments may be longer for some patients.

Analysis of predicted versus actual utilisation

This analysis compares the predicted and actual use of botulinum toxin for the treatment of chronic migraine.

Table 4: Predicted vs Actual analysis

		Year1	Year 2	Year 3
		Mar14 to Feb15	Mar15 to Feb16	Mar16 to Feb17
Initiating patients	Predicted (P)	[redacted]	[redacted]	[redacted]
	Actual (A)[a]	3,517	2,881	2,524 (YTD)**
	% Difference (A-P)/P	[redacted]	[redacted]	[redacted]
Prevalent patients[#]	Actual (A)[a]	3,517	5,444	6,542 (YTD)**
Number of PBS treatments / prescriptions (including RPBS)^	Predicted (P)	[redacted]	[redacted]	[redacted]
	Actual (A)[b]	7,631	14,580	17,267 (YTD)*
	% Difference (A-P)/P	[redacted]	[redacted]	[redacted]
Number of MBS services (not including services for DVA patients)	Actual (A)[a]	7,826	13,873	14,206 (YTD)**
	% Difference [c] (A-P)/P	+125%	+64%	na
Number of vials	Predicted (P)	[redacted]	[redacted]	[redacted]
	Actual (A) [b]	14,081	27,894	33,306*
	% Difference (A-P)/P	[redacted]	[redacted]	[redacted]
Mean vials per treatment/prescription	Predicted (P)	2.00	2.00	2.00
	Actual (A)[b]	1.85	1.91	1.93*
	% Difference (A-P)/P	-8%	-4%	-4%

[a] ascertained from MBS data for item 18377. See methods section for details.
[b] ascertained from PBS data
[c] compared to the predicted number of PBS treatments / prescriptions
[#] the predicted estimates of use did not quantify prevalent patients
* Year to date (Dec 16)
** Year to date (Nov 16)
^ RPBS was 0.39% of all prescriptions.

Table 4 shows that utilisation has been much higher than predicted.

The higher than expected number of patients treated could be due to an underestimate of the pool of eligible patients or a higher rate of uptake in eligible patients. [redacted] There is limited evidence available to assess the reasons for any difference, and the risk sharing arrangement was developed to address this uncertainty.

One assumption that can be tested is the proportion of neurologists who inject botulinum toxin. The resubmission assumed that 25.3% of neurologists would inject botulinum toxin (based on the proportion who were registered to inject botulinum toxin), and that this figure would increase by 2% per year. This means that it was expected that 31.3% of neurologists would inject botulinum toxin in 2016.

The total number of PBS claiming neurologists was counted from the PBS prescription data which contains a prescriber ID variable. There were 609 neurologists that prescribed at least one PBS prescription of any drug in 2016, and 156 (25.6%) of these prescribed botulinum toxin for chronic migraine in 2016. The number of neurologists who prescribed botulinum toxin for any indication was 186 (30.5%). This finding suggests that the higher than expected number of patients treated cannot be accounted for by an increase in the proportion of neurologists offering botulinum treatment.

The difference in predicted and actual use is disproportionate across the number of patients and the number of prescriptions. For example, in the first year of listing the number of patients starting treatment was 54% higher than expected but the number of prescriptions was approximately 120% higher than expected. Possible reasons for the disproportionate difference between patients and prescriptions could include:

- The number of prescriptions in year 1 for patients who had received botulinum toxin through the private market prior to PBS listing may have been underestimated because these patients would have already demonstrated a response;
- The rate of continuation in the first and subsequent years of a patient's treatment, and therefore the number of prescriptions supplied, may be higher than expected. Continuation rates are investigated further below.
- The "half year correction" applied to the estimates in year 1 was based on the assumption the patients would initiate evenly throughout the year. However a higher proportion of patients initiated earlier in the listing year (see Figure 2). Note that Q2 in 2014 only contains one month of data, March 2014, so the first year of listing is approximately 2014 Q2 to 2015 Q1.

The recommended dose for treating chronic migraine is 155 U to 195 U, therefore requiring two 100 U vials. The mean number of vials per treatment was slightly lower than predicted. One possible reason for this may be that some patients only used one vial. In the submission to the July 2013 PBAC (p27) the sponsor had noted that some patients paying for botulinum toxin privately prior to PBS listing were treated at a lower dose of 100 U due to cost. Another possibility is that vials were shared between patients in clinics, however PBS-subsided botulinum toxin vials must not be split across patients as multi-use is not permitted under PBS Regulations. Table 5 shows the distribution of the number of vials per prescription for all prescriptions from September 2015 to the end of December 2016.

Table 5: Distribution of the number of vials per prescription for chronic migraine

Number of vials	% Prescriptions
1	8.53%
2	90.79%
3	0.43%
4	0.25%
Total	100.00%

Table 5 shows that even though the maximum quantity in the PBS listing is 4 vials, neurologists are appropriately prescribing 2 vials (or occasionally one vial) in accordance with the usual dose for this indication.

Treatment Continuation Rate

The predicted continuation rate at week 24 (i.e. after the 2nd treatment) in the June 2012 resubmission was 32.9% based on the pooled response rate in the population in the PREEMPT trial that had received 3 prior prophylactic medicines. Continuation after this was arbitrarily predicted to be 80% every 24 weeks.

Continuation rates were assessed using MBS service data (Item 18377) for injection of botulinum toxin for chronic migraine as the patient level PBS data is incomplete. Figure 3 shows the continuation rate for patients who initiated botulinum toxin for chronic migraine between 1 September and 30 November 2014. Patients who claimed their first MBS service in the first 6 months of listing (1 March to 31 August 2014) were not included as they may have been grandfathered from non-MBS funded treatment and may have already been assessed for treatment response. All initiators in the cohort were given equal follow up of exactly 24 months from each patient's initiation date to eliminate any confounding that could result from unequal follow up. The initiators from December 2014 onwards were not included as they had less than 24 months follow up.

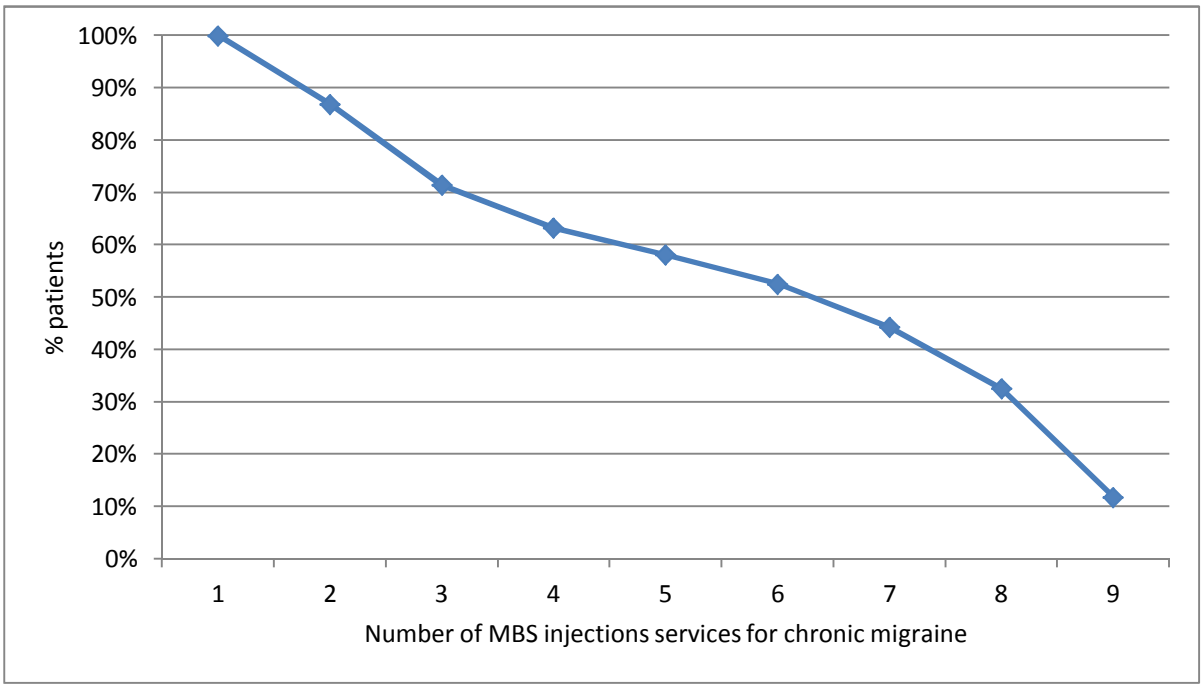

Figure 3: Continuation on botulinum toxin treatment for chronic migraine for patients initiating between 1 September and 30 November 2014 (n=795).

Note: Each patient was followed for exactly 24 months from the date of their first service. The continuation rate for the higher number of services (e.g. 7, 8 and 9) is artefactually low as some patients, who had longer than average between treatments, would have these services after 24 months

In Figure 3 the continuation rate after 24 weeks, defined as the percent of patients that had a 3rd injection, was 71.4% which is approximately double that predicted from the clinical trial (32.9%).

The continuation rate after 48 weeks, defined as the percent of patients that had a 5th injection, was 58.1%. This implies a continuation rate between 24 and 48 weeks of 58.1% / 71.4% = 81.4%. This is approximately equal to the predicted ongoing continuation rate of 80% every 24 weeks, albeit from a higher starting point.

In the July 2013 resubmission, continuation rates (treatments per year) were derived from the economic model. It was estimated that patients would use 3.05 prescriptions based on the 50% reduction in headache days response criterion in the first year of treatment. When a 30% reduction in headache days was used as the response criteria, it was predicted that patients would use 3.54 prescriptions in the first year of treatment.

To assess these assumptions, the number of MBS injection services for chronic migraine in the first 12 months after initiation was calculated for each patient. The median was 4 and the mean was 3.23 services.

Migraine medications supplied prior to initiation of Botox for chronic migraine

The PBS restriction requires that patients must have failed, be intolerant or contraindicated to at least three prophylactic migraine medicines to be eligible for botulinum toxin. Propranolol, amitriptyline, methysergide, pizotifen, cyproheptadine or topiramate are the prophylactic migraine medications specified in the restriction.

To assess compliance with the restriction an analysis of prior medicines was undertaken. DUSC had also previously suggested that analysis of other migraine therapies (at a patient level) would provide insight into whether the use of botulinum toxin is for chronic migraine (June 2016).

Migraine medications were divided into the following groups for this analysis;

- Botulinum toxin type A
- Botulinum Toxin Type A pre-requisite prophylactic migraine drugs listed in the PBS restriction for chronic migraine.
- Other prophylactic migraine medicines recognised for use in Australia[5,6]

Table 6: Classification of medicines

Drug group	ATC code	Drug name
Botulinum toxin type A	M03AX01	botulinum toxin type A
Botulinum toxin pre-requisite prophylactic migraine drugs	N03AX11	topiramate
	N06AA09	amitriptyline
	C07AA05	propranolol
	N02CX01	pizotifen
	N02CA04	methysergide
	N02CX	cyproheptadine
Other prophylactic migraine drugs	C08DA01	verapamil
	C07AB03	atenolol
	C07AB02	metoprolol
	N03AG01	valproate
	C09CA06	candesartan (plain form only)
	C09AA03	lisinopril (plain form only)
	N02BG	gabapentin
	C02AC01	clonidine

Under previous administrative arrangements for the Botulinum Toxin Program, the data did not include a patient identifier and cannot be used for this analysis. Therefore the MBS service data was linked to PBS data allowing the number of prophylactic therapies prior to a patient's first service for injection of botulinum to be assessed. The patient cohort analysed initiated botulinum toxin from 1 April to the 30 November 2016.

[5] Stark and Stark. Migraine prophylaxis. MJA 2008; 189: 283–288
[6] Australian Medicines Handbook Pty Ltd (2017)

An important limitation to be considered when interpreting this analysis is that there is likely to be missing data because many prophylaxis medicines are priced under the general patient copayment. Undercopayment PBS prescriptions data for general patients is only available from April 2012. Of the six drugs listed as prophylactic agents in the restriction, four were priced under the general copayment prior to April 2012. Of the eight drugs in the "Other prophylactic migraine drugs" group, seven were priced under the general copayment prior to April 2012. Given the chronic nature of this condition (patients in the PREEMPT clinical trial had a mean duration since onset of chronic migraine of 18−21 years) it is likely that some medicines trialled by general patients will be missing in the available PBS data.

To investigate this issue further the percentage of patients in the cohort with only General patient scripts in a year was determined for the years prior to the collection of under-copayment data. From 2003 to 2011 approximately 50% of all patients in the cohort had only general scripts in each year, thus it is likely that the percentage of patients estimated to have fulfilled the restriction requirement will be a significant underestimate.

A concessional only cohort was considered, however thought unlikely to be representative because it is may be biased toward those people more severely affected by chronic migraine and unable to work.

Another limitation is that some of these prophylactic medicines are available over the counter (e.g. cyproheptadine) or on private prescription (e.g. gabapentin is not on the PBS for migraine).

The cohort (patients who commenced botulinum toxin from 1 April to the 30 November 2016) was chosen to maximise the look back period where there was undercopayment prescription capture in the PBS data (i.e. from April 2012). Thus there was at least a 4 year lookback across PBS data with complete capture and then a further lookback from March 2012 to January 2003 where there was incomplete capture for PBS items priced under the general copayment.

The results of the analysis are provided in Figure 5.

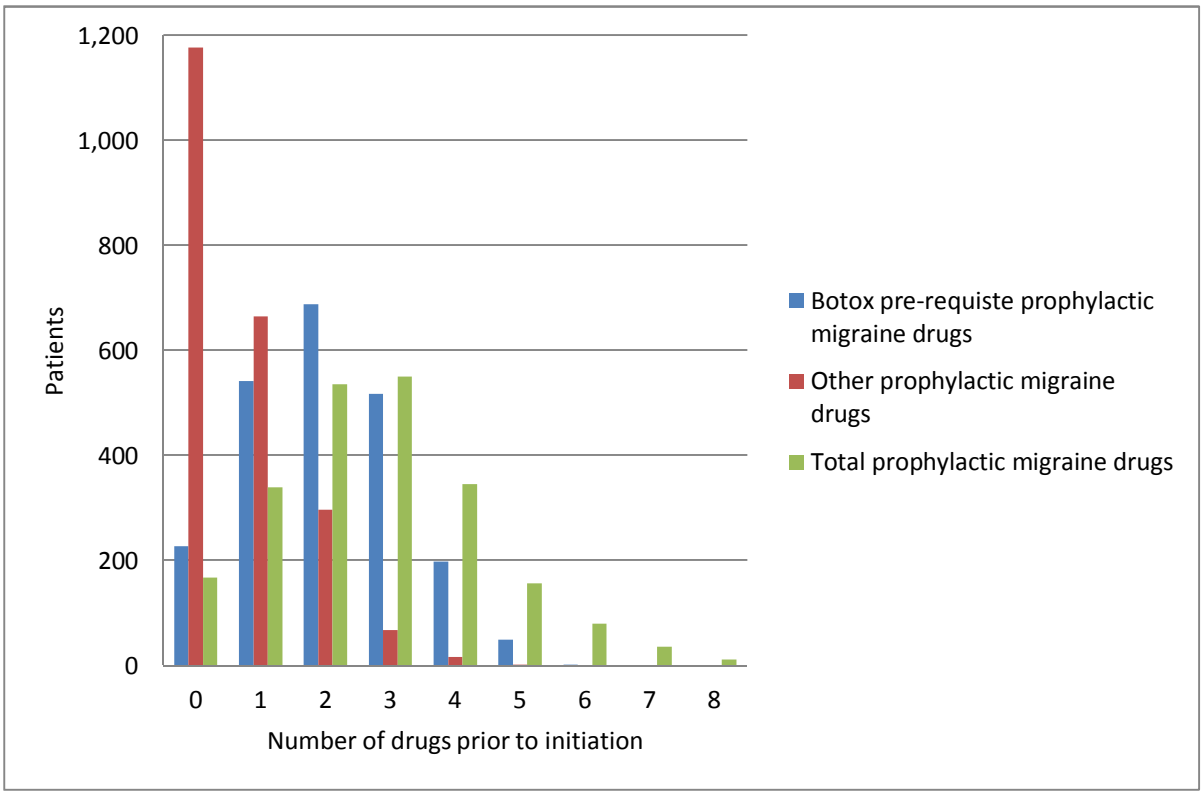

Figure 5: Distribution of the number of prior PBS drugs for patients initiating botulinum toxin for chronic migraine from April to the end of November 2016.

Figure 5 shows that 34.5% of patients had evidence in their PBS prescription history of 3 or more Botox restriction pre-requisite prophylactic migraine drugs and 53% of patients had 3 or more prophylactic migraine drugs in total.

Even if the PBS data were complete and the estimate was accurate, it would not take into account the patients that were contraindicated to some of the drugs, as these patients would not have been prescribed these drugs.

The DUSC is requested to advise whether it is worthwhile to retain this analysis in the report when it is published as DUSC Public Release Document on pbs.gov.au

Analysis by State

Figure 6 shows the number of patients that received an MBS service for the injection of Botox for chronic migraine from December 2015 to the end of November 2016 (the most recent year of MBS data) and patient State. The patient State was based on the patient's Medicare enrolment address at the time the service was processed by DHS.

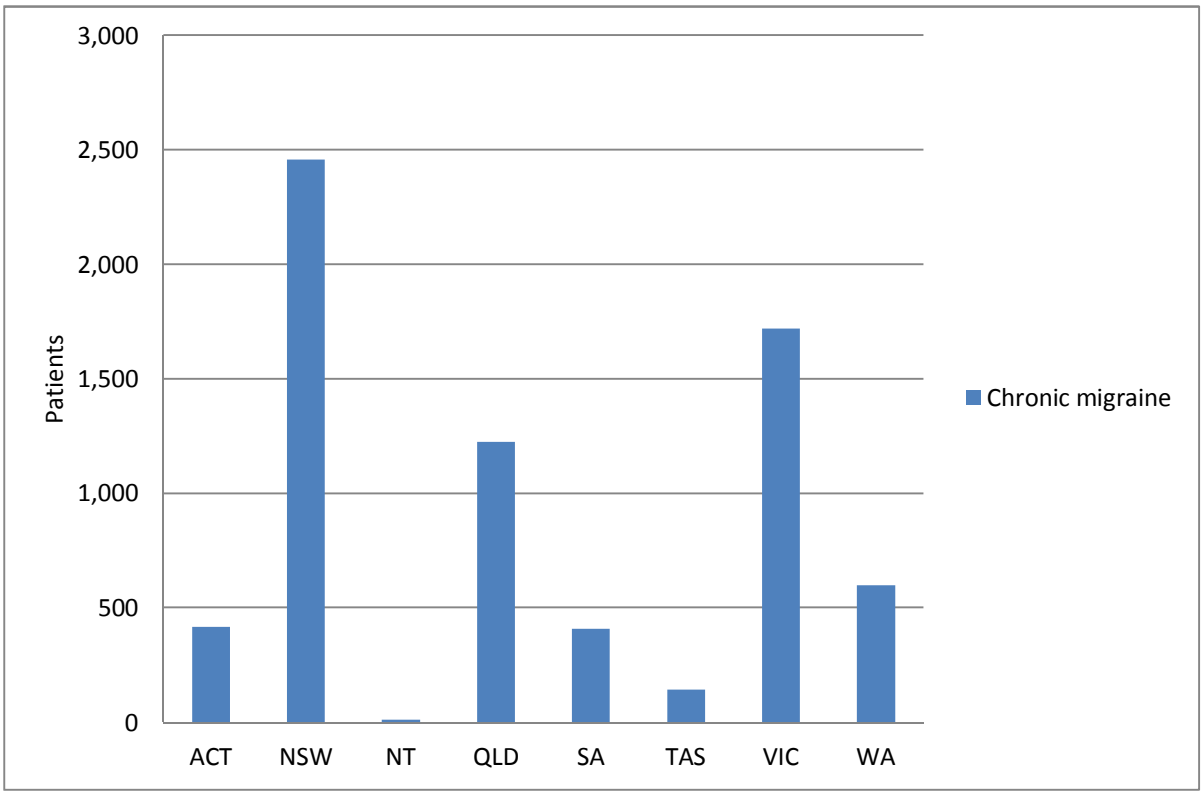

Figure 6: Patients that received an MBS service for the injection of Botox for chronic migraine from December 2015 to the end of November 2016 by patient state.

Figure 7 shows the Figure 6 data converted to a treatment rate (i.e. patients as a % of the state population[7])

[7] 3101.0 - Australian Demographic Statistics, Sep 2016, http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3101.0Sep%202016?OpenDocument

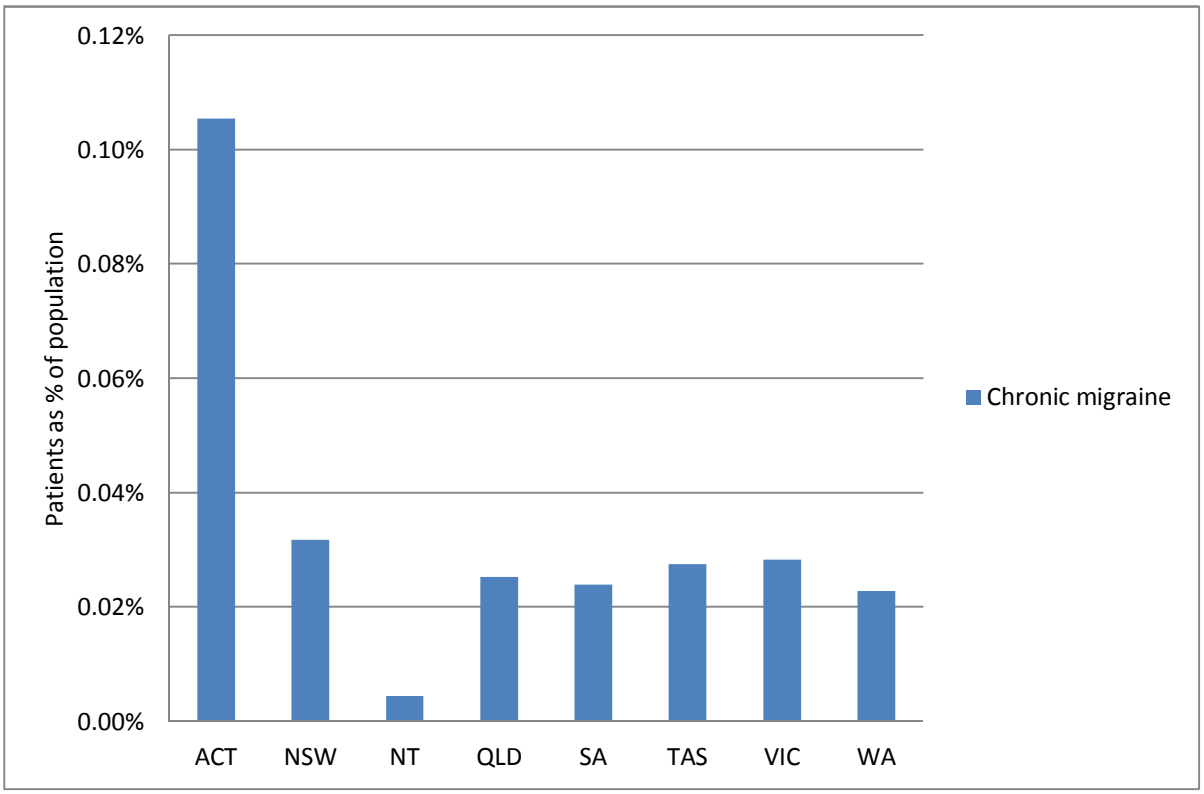

Figure 7: Treatment rate (patients as % of population) for the injection of Botox for chronic migraine from December 2015 to the end of November 2016

The treatment rates in most states were similar with approximately 23-32 patients per 100,000. Treatment rates were substantially higher in the ACT (105 per 100,000) and substantially lower in the NT (5 per 100,000).

The number of botulinum toxin providers (prescribers) per capita was also investigated and it was found that the ACT has a similar number of prescribers per capita to the other States for the chronic migraine indications. This means that the increased treatment rate in the ACT was due to prescribers treating more patients each rather than a higher number of prescribers per capita.

The above analyses (i.e. Figure 6 & 7) were repeated using the PBS prescription data for 2016 and the results were very similar.

Risk Sharing Arrangement

To manage uncertainty in the financial estimates, to address concerns with potential usage beyond the restriction and the expected difficulty differentiating use within and beyond the intent of the restriction (see page 6), a risk sharing arrangement was agreed.

[redacted]

Discussion

The utilisation of botulinum toxin for migraine has been substantially higher than estimated. This is due to more patients treated, but to a greater extent, is driven by high rates of continuation on treatment.

Size of the eligible population

There was considerable uncertainty in estimating the size of the eligible population and uptake rates for botulinum toxin as identified by the DUSC and the PBAC, and acknowledged by the sponsor. *It is possible that the size of the eligible population was underestimated. To our knowledge there are no new relevant prevalence studies to verify that this is the case. The higher than expected number of patients does not appear to be due to an increase in the number of neurologists providing botulinum toxin, although it is possible that treatment throughput has improved with increased experience in use of botulinum toxin from this indication.*

Commencement of botulinum as an earlier line therapy is also a possible reason for the higher number of patients. The recommendation to list botulinum toxin was based on acceptance of best supportive care as the appropriate comparator for patients who have failed at least three lines of therapy. *An analysis to investigate whether patients are commencing botulinum toxin after failure of three oral prophylactic medicines was inconclusive because of data limitations. Similarly, assessing whether medication overuse headache has been managed prior to commencing botulinum toxin from PBS data is challenging because many acute treatments are available over the counter or may be provided on private prescription.*

A further concern raised by PBAC was a risk that PBS subsidised botulinum toxin may be used in other chronic headache indications or for cosmetic effects. *While these risks remain, the limitation to neurologists may minimise risks for different headache types or for cosmetic use.* The sponsor, in the May 2012 pre-subcommittee response, noted that chronic migraine and chronic tension type headache (CTTH) are distinct conditions, that neurologists are able to differentiate, and referenced a published meta-analysis indicating

that botulinum toxin is not effective for tension headache or episodic migraine.[8] The sponsor had reasoned that the closest medical indication to cosmetic use, blepharospasm, which is PBS listed for a broader group of specialties than just neurology, had steady predictable annual claims indicative of responsible usage (May 2013 pre-subcommittee response). *While PBS subsidised botulinum toxin may be initiated in patients meeting the eligibility criteria for chronic migraine, cosmetic effects may be a factor contributing to the high continuation rates.* As described by Rothrock 2012, botulinum toxin *"will cause paralysis of the muscles into which it is injected, and patients may note associated smoothing of forehead wrinkles and some difficulty in voluntarily lifting the eyebrows; when present, these particular effects tend to vanish within 3 to 4 months".*[9]

Treatment Continuation

The PBAC expressed considerable concern that there would be continued use of botulinum toxin in partial responders although acknowledged that the invasive nature of botulinum toxin administration may serve to limit use in partial and non-responders. *The very high continuation rates, approximately double that compared with clinical trial response rates after 2 treatments, could indicate that botulinum is being continued in patients achieving some improvement but who are not fulfilling the criteria of a 50% reduction in headache days. There is likely to be differences between clinical trial and real world setting reporting of the reduction in headache days per month, particularly given the subjective nature of this outcome.*

The modelled number of treatments per year from the July 2013 resubmission resulted in a higher number of prescriptions than the trial based continuation rates. The PBAC had raised a number of issues with the economic evaluation including the transition probabilities and the extrapolation of the incremental treatment effect of botulinum toxin beyond the trial duration to 5 years in the absence of supportive evidence. As outlined in Section F of the submission to the July 2012 PBAC, a single arm open label postmarketing study, COMPEL (NCT01516892) to evaluate the long-term efficacy, safety, and tolerability study of BOTOX® in patients with chronic migraine was expected to be completed in March 2016. The study was designed to evaluate the 155 U (fixed site, fixed dose) PREEMPT regimen given every 12 weeks for 2 years (a total of 9 treatment cycles). The study was expected to include patients from five Australian sites. *The sponsor may wish to provide the PBAC with the final results of this study via the pre-DUSC response*.

Other matters

Methysergide was discontinued by the manufacturer in October 2013 (no longer on the Australian market) and delisted from the PBS from 1 May 2014. *The PBAC may wish to consider whether this medicine should be deleted from the list of prophylactic medicines in the botulinum toxin restriction.*

[8] Jackson JL et al. Botulinum Toxin A for Prophylactic Treatment of Migraine and Tension Headaches in Adults: A Meta-analysis. JAMA 2012;307(16):1736-1745

[9] Rothrock 2012. Headache Toolbox. American Headache Society. doi: 10.1111/j.1526-4610.2011.01880.x

Typographical errors in the spelling of amitriptyline, propranolol and methysergide in the restriction for botulinum toxin have been noted and will be corrected in future versions of the PBS schedule.

There were differences in treatment rates across the states, with the treatment rate in the ACT more than triple that for any other state or territory. *Treatment rates presented in this report are based on the state of the patient Medicare enrolment address. Therefore treatment by a provider, or supply or distribution by a pharmacy in a different state, does not account for these differences.*

DUSC consideration

The DUSC considered that:

- Use of botulinum toxin was substantially higher than predicted. There are a higher than predicted number of initiating patients but the key driver was the higher than expected continuation rates.
- The proportion of neurologists that administered botulinum toxin for chronic migraine was very close to that predicted, so this was not a factor in the higher than predicted use.
- Data limitations meant that it was not possible to determine whether or not use is occurring earlier in the treatment algorithm than proposed in the submission (i.e. before experiencing an inadequate response, intolerance or a contraindication to three or more prophylactic migraine medicines).
- The mean number of vials per treatment analysis suggests that the dose used is consistent with recommendations.
- There may be QUM concerns associated with the continuation rate being double (i.e. 71.4%) that predicted from the pooled data of the PREEMPT trial (i.e. 32.9%). DUSC considered the high continuation rate was due to use in partial responders. However, DUSC noted that in its PSCR the sponsor presented medical chart audit data from seven clinicians that indicated that 73.9% of patients achieved the PBS continuation criterion of 'achieved and maintained a 50% or greater reduction from baseline in the number of headache days per month after two treatment cycles'. The difference between the trial and real world continuation rates may be the subjective nature of the assessment (headache days), the lack of alternative treatments or the patients appreciation of the cosmetic effects of the treatment.
  Another QUM issue is that partial responders may be unnecessarily exposed to the adverse effects of botulinum toxin. Compared with best supportive care, statistically significant differences were found for eyelid ptosis (3.5% vs. 0.3%), neck pain (9.0% vs. 2.7%), musculoskeletal stiffness (3.2% vs. 0.9%), muscular weakness (5.5% vs. 0.3%) and myalgia (3.1% vs. 0.9%) in PREEMPT trials.[10]
- The government expenditure associated with the higher than expected use has been managed effectively by the Risk Share Agreement. If the sponsor were to request a change to the RSA, a submission to the PBAC would be required to justify this.

[10] *Botulinum Toxin Type A, injection, 100 units/vial, Botox® Public Summary Document, July 2013 PBAC Meeting*

- There was no apparent reason for the substantially higher treatment rates of patients in the ACT. It was pointed out that there is, in addition, a processing anomaly where most of the botulinum toxin prescriptions in Australia are dispensed through a hospital pharmacy in the ACT. However, the Secretariat clarified that the analysis in the report was based on patient location and so should not be affected by the dispensing arrangements. DUSC considered that further investigation into utilisation in the ACT appears warranted. The Department advised of referral of this matter to the compliance area.
- The use of MBS data to supplement the patient level analysis was valid and useful for the predicted vs actual analysis. In particular it enabled the count of patients since the listing of botulinum toxin for chronic migraine and patient's initiation date for the purpose of assessing prior prophylactic migraine medicines.

DUSC actions

The report, Sponsor response, and DUSC minutes were referred to the PBAC noting:

- Methysergide was discontinued by the manufacturer in October 2013 (no longer on the Australian market) and delisted from the PBS from 1 May 2014. The PBAC may wish to consider whether this medicine should be deleted from the list of prophylactic medicines in the botulinum toxin restriction.

A response received from the Australian and New Zealand Association of Neurologists was also provided to the PBAC.

Context for analysis

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines.

The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC.

The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits and risks of medicines.

The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

Sponsors' comments

Allergan: The sponsor has no comment.

Disclaimer

The information provided in this report does not constitute medical advice and is not intended to take the place of professional medical advice or care. It is not intended to define what constitutes reasonable, appropriate or best care for any individual for any given health issue. The information should not be used as a substitute for the judgement and skill of a medical practitioner.

The Department of Health (DoH) has made all reasonable efforts to ensure that information provided in this report is accurate. The information provided in this report was up-to-date when it was considered by the Drug Utilisation Sub-committee of the Pharmaceutical Benefits Advisory Committee. The context for that information may have changed since publication.

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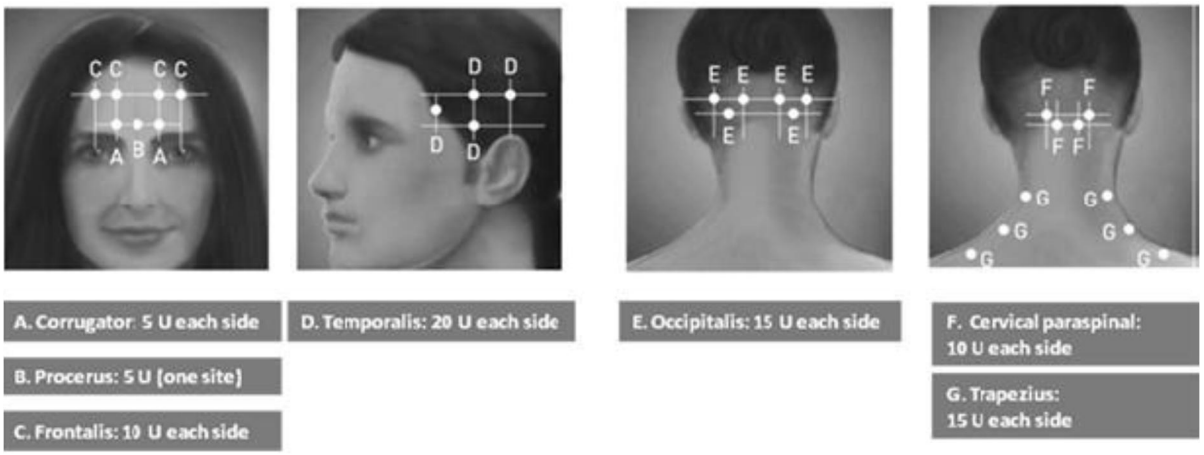
Appendix A: Administration of Botox for chronic migraine

The recommended dose for treating chronic migraine is 155 U to 195 U administered intramuscularly (IM) using a 30-gauge, 0.5 inch needle as 0.1 ml (5 U) injections per each site. Injections should be divided across 7 specific head/neck muscle areas as specified in the table below. A 1-inch needle may be needed in the neck region for patients with extremely thick neck muscles. With the exception of the procerus muscle, which should be injected at 1 site (midline), all muscles should be injected bilaterally with the minimum dose per muscle as indicated below, with half the number of injections sites administered to the left, and half to the right side of the head and neck. If there is a predominant pain location(s), additional injections to one or both sides may be administered in up to 3 specific muscle groups (occipitalis, temporalis and trapezius), up to the maximum dose per muscle as indicated in the table below.

Recommended injection sites for chronic migraine:



BOTOX® Dosing By Muscle for Chronic Migraine

	Recommended Dose
Head/Neck Area	**Total Number of Units (U) (number of IM 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 Muscle Group[b]	20 U (4 sites)
Total Dose Range:	**155 U to 195 U**

[a] 1 IM injection site = 0.1 mL = 5 U BOTOX

[b] Dose distributed bilaterally for minimum dose