

## 7.02 BOTULINUM TOXIN TYPE A purified neurotoxin complex, Lyophilised powder for injection, 100 units, Botox<sup>®</sup>, Allergan Pty Ltd

### 1 Purpose of Application

- 1.1 The submission was lodged to provide support for the sponsor's request to revise the risk sharing arrangement (RSA) relevant to the use of botulinum toxin type A (hereafter named Botox) under its PBS listing for the treatment of chronic migraine. Detail on the requested change to the RSA is provided below under 'Estimated PBS usage and financial implications'; in brief [REDACTED]
- 1.2 A retrospective chart review of Australian patients with chronic migraine (Stark 2017; N=211) served as the key evidentiary basis of the requested RSA revision.

**Table 1: Key components of the clinical issue addressed by the submission**

Component	Description
Population	Adults with chronic migraine
Intervention	Botulinum toxin, delivered by injection every 12 weeks to 31 sites in the head and neck along with 8 'follow the pain' sites. Botulinum toxin is a last line therapy after patients have failed to achieve an adequate response or are intolerant or contraindicated to at least 3 oral prophylactic medications.
Comparator	Best supportive care (BSC)
Outcomes	Proportion of patients with $\geq 50\%$ reduction in the number of headache days per month
Clinical claim	The submission stated that in the PBS population treated with Botox for chronic migraine (Stark 2017 retrospective chart review), patients achieved better clinical outcomes than those achieved by patients in the pivotal trials (PREEMPT trials). The submission used this claim to support its proposed revision to the RSA.

Source: Sections 1 and 2 of the submission.

### 2 Current listing

- 2.1 The current listing for Botox for the treatment of chronic migraine is provided below.

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
BOTULINUM TOXIN TYPE A 100 units injection, 1 vial	1	4	0	\$1,626.07 published price \$ [REDACTED] effective price	BOTOX AG

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<b>Condition:</b>	Chronic migraine
<b>Restriction:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	Must be treated by a neurologist.
<b>Clinical criteria:</b>	<p>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.</p> <p>AND</p> <p>Patient must have experienced an inadequate response, intolerance of a contraindication to at least three prophylactic migraine medications prior to commencement of treatment with botulinum toxin type A neurotoxin.</p> <p>AND</p> <p>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.</p> <p>AND</p> <p>Patient must be appropriately managed by his or her practitioner for medication overuse headache, prior to initiation of treatment with botulinum toxin.</p>
<b>Population criteria:</b>	Patient must be aged 18 years or older.
<b>Prescriber Instructions:</b>	Prophylactic migraine medications are propranolol, amitriptyline, methysergide, pizotifen, cyproheptadine or topiramate.
<b>Administrative Advice:</b>	Special pricing arrangements apply.

- 2.2 The ESC noted that the sponsor requested that, if the PBAC were not of a mind to accept the proposed amendments to the RSA, then the PBAC should instead consider increasing the authority level to a written authority for both initiation and continuation. The sponsor also indicated a willingness to use a combination of these two approaches. The PBAC considered that the concerns raised in the submission regarding reimbursement were not a valid reason for increasing the authority level for this item.

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

### 3 Background

#### **Registration status**

- 3.1 Botox was TGA registered for use in chronic migraine on 15 March 2011. Botox also has TGA registration for the treatment of: strabismus, blepharospasm, focal spasticity, spasmodic torticollis, severe primary hyperhidrosis, spasmodic dysphonia, urinary incontinence, overactive bladder and appearance of upper facial rhytides (glabellar lines, crow’s feet and forehead lines).

#### **Previous PBAC consideration**

- 3.2 While there has been no previous PBAC consideration of the sponsor’s request to revise the RSA, there were three major submissions to the PBAC, in November 2011, July 2012 and July 2013, seeking PBS listing of Botox for the treatment of chronic

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migraine. A positive recommendation was received in July 2013 and Botox was PBS-listed for chronic migraine in March 2014. A summary of the previous submissions is provided below.

**Table 2: Summary of the three Botox submissions for chronic migraine**

Component	November 2011	July 2012	July 2013
Requested listing	Failure of ≥2 prior prophylaxis medications. Continuation based on ≥30% reduction in headache days/month by week 24.	Failure of ≥3 prior prophylaxis medications. For continuation: option 1: ≥50% decrease in headache days/month by week 24 or option 2: ≥50% decrease in HA days/month by week 24 or ≥30% decrease in moderate/severe headache days/month by week 24.	Failure of ≥3 prior prophylaxis medications. Continuation based on ≥ 50% reduction in headache days/month by week 24.
Requested price	\$ [REDACTED] /vial	\$ [REDACTED] /vial	\$ [REDACTED] /vial
Clinical evidence	PREEMPT 1 and II, which were randomised, double-blind, open-label trials comparing Botox and placebo.		PREEMPT I and II plus Cady 2012 which was a Phase IV randomised, double-blind, cross-over trial in 20 patients.
Clinical claim	Botox as superior in terms of comparative effectiveness and inferior in terms of comparative safety over best supportive care		
Economic model	Markov cohort model with 6 health states based on number of headache days per 28 days. 5 year duration.		
ICER	\$ [REDACTED] /QALY	\$ [REDACTED] /QALY	\$ [REDACTED] /QALY
Financial estimates	\$ [REDACTED] patients over 5 years net cost to Government	\$ [REDACTED] patients over 5 years net cost to Government	\$ [REDACTED] patients over 5 years net cost to Government
RSA	Not specified.	[REDACTED] rebate on Botox price. [REDACTED]	[REDACTED] rebate on Botox price. [REDACTED]
PBAC decision	Reject	Reject	Recommend

Source: botulinum toxin COM 6-1 11-11; Botox migraine COM 7-2 07-12; 7-1 botulinum toxin COM 07-13.

3.3 In July 2013, the PBAC considered the number of patients continuing treatment may be higher than assumed by the re-submission, as “headache days” is a subjective outcome, and if patients perceive an improvement they may be more likely to want to continue treatment. The PBAC considered there was considerable risk of use beyond the proposed restriction in partial responders, although acknowledged that the invasive nature of botulinum toxin administration may serve to limit use in partial and non-responders (Section 11, Botulinum Toxin Type A PBAC PSD, July 2013).

3.4 In July 2013, the PBAC recommended extending the current Section 100 Botulinum Toxin Program listing for botulinum toxin type A to include prophylaxis of headaches in adults patients with chronic migraine who meet certain criteria, on the basis of acceptable cost-effectiveness compared to best supportive care. To address

uncertainty in the cost-effectiveness being reflected in practice, the PBAC recommended that a tighter RSA be negotiated with the sponsor, [REDACTED] based on the smaller estimates of use provided in the July 2012 re-submission (Section 11, Botulinum Toxin Type A PBAC PSD, July 2013).

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **4 Population and disease**

- 4.1 To be eligible for treatment through the PBS for chronic migraine, a 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 treatment with Botox. The patient must have also experienced an inadequate response, intolerance or a contraindication to at least 3 prophylactic medications prior to commencing treatment with Botox, and be treated by a neurologist.
- 4.2 Chronic migraine is thought to be associated with reduced quality of life, increased healthcare expenditure and more frequent comorbidities relative to episodic migraine.

## **5 Comparator**

- 5.1 The previously accepted comparator for Botox for the treatment of chronic migraine was best supportive care (BSC) (Section 6, Botulinum Toxin Type A PBAC PSD, July 2013).
- 5.2 The majority of clinical evidence presented in the current submission comprised single arm studies, and the pivotal new study is a retrospective chart review (Stark 2017). The submission nonetheless applied the results of the Stark 2017 retrospective chart review to the economic model, comparing a PBS population to the BSC arm in the model (which had been sourced from a randomised controlled trial). The PBAC considered the informativeness of this comparison was limited given demographic, disease characteristics and trial/study protocol differences between the two data sources (see 'Comparative effectiveness' below).

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician outlined the impact of chronic migraine on patients' quality of life and highlighted that those with the condition were at increased risk of analgesic dependence. The clinician highlighted the potential benefits Botox provided to patients and noted that its use was just one element of an individualised treatment plan. An overview of the Stark 2017 retrospective chart review was provided, and the clinician addressed other matters in response to the Committee's questions.

**Consumer comments**

- 6.2 The PBAC noted and welcomed the input from individuals (4) and health care professionals (6) via the Consumer Comments facility on the PBS website. The comments highlighted the impact of chronic migraine on patients' quality of life. They also described a range of benefits of treatment with Botox including a reduction in the frequency and severity of migraine along with a reduction in analgesic use.

**Clinical trials and non-randomised studies**

- 6.3 The focus of the submission was 'real-world' evidence, specifically all evidence when Botox was used for the treatment of chronic migraine, consistent with TGA-approved dosing recommendations, in real-world clinical practice settings.
- 6.4 The 14 selected studies of real-world evidence varied in design, but with the exception of one randomised controlled trial (n=1), all were non-randomised and included post-marketing or post-authorisation studies (n=4), retrospective chart or insurance database reviews (n=4), or prospective observational studies (n=5).
- 6.5 The submission provided brief summaries of study design and results for the 14 selected studies and provided detailed information for one of the studies, Stark 2017. The submission focused on the Stark 2017 retrospective chart review as it was an Australian study based on a sample of patients with chronic migraine treated with Botox following its listing on the PBS. Data from the Stark 2017 retrospective chart review was used to update the economic model (see 'Economic analysis' below). The PBAC considered that the key study used to support this submission was underreported as it was based on a poster accompanied by an abstract.
- 6.6 A brief summary of the 14 identified real-world studies is provided in the table below, with citation details for the Stark 2017 retrospective chart review in the following table.

**Table 3: Key features of the ‘real-world’ studies identified in the submission**

Study	N	Location	Design	Risk of bias
191622-110	1,160	Europe	Post-authorisation, open-label, observational, multicentre.	Not assessed by the submission. Risk of bias would be high.
191622-139	672	South Korea	Post-marketing surveillance.	
COMPEL	715	USA, Australia, South Korea	Post-authorisation, open-label, multicentre.	
Dominguez 2016	553	Spain	Observational, open-label, multicentre.	
FORWARD	282	USA	Randomised, cross-over, open-label (Botox and topiramate).	
Hepp 2016	3,840	USA	Retrospective review insurance claims.	
Hull Migraine Clinic 2015	465	UK	Observational, open-label.	
Maasumi 2015	359	USA	Retrospective chart review.	
Negro 2016	275	Italy	Observational, open-label, multicentre.	
PREDICT	191	Canada	Observational, open-label, multicentre.	
REPOSE	633	Europe, Russia	Post-marketing surveillance.	
Rothrock 2016	310	USA	Observational, open-label.	
Santoro 2017	207	Italy	Retrospective chart review.	
Stark 2017	211	Australia	Retrospective chart review.	Moderate as rated by the submission using ROBINS-I.

Source: Table 2-8, p55-60 of the submission.

**Table 4: Trials and associated reports presented in the submission for Stark 2017**

Trial ID	Protocol title/ Publication title	Publication citation
Stark 2017	Stark C et al. The real-world efficacy of botulinum toxin type a (BOTOX®) for the prophylaxis of headaches in adult patients with chronic migraine in Australian clinical practice: A retrospective chart review.	Journal of Neurology, Neurosurgery and Psychiatry 2017; 88(5): e22-e23.

Source: Table 2-4, p41-48 of the submission.

6.7 The submission stated that the ROBINS-I tool was used to assess risk of bias in the Stark 2017 retrospective chart review and that the study was considered to be at low or moderate risk of bias for all domains. However, the PBAC considered that there are some aspects of the study that indicate it has a high risk of bias, these include:

- The study was uncontrolled and unblinded. In addition, there are potential methodological risks associated with retrospective chart reviews that were not addressed in the submission.
- The primary outcome in the Stark 2017 retrospective chart review matched the PBS continuation criteria — a 50% reduction in the number of headache days per month following two Botox treatment cycles. The submission did not provide any information on how headache days were defined or assessed in the study. The Pre-Sub-Committee Response (PSCR) stated the definition of headache days was identical to that in the PREEMPT trials and provided the Stark 2017 protocol for information on assessment. The protocol stated that data was “extracted from the patient charts and patient HA [headache] diaries of approximately 200-250 eligible CM [chronic migraine] patients”. Of the patients included in the trial (N=211), response rates were assessed using a headache diary for 48.8% (N=103)

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of the trial population. For the other 51.2% of patients, the trial protocol indicated that headache days could be recorded by the physician, but no further information on how this was assessed was provided. The submission did not detail whether or how any coding procedures may have been used in review of patient charts and whether accuracy in terms of intra- and inter-rater reliability was checked.

- The Stark 2017 retrospective chart review was funded by the sponsor. While the poster stated that no honoraria or payments were made for authorship, there remains a risk of bias.
- The Stark 2017 retrospective chart review was conducted in the Australian PBS-eligible population where eligibility for PBS-subsidised Botox for the treatment of chronic migraine is dependent on the patients meeting a continuation rule. The ESC noted that there is some evidence that a PBS continuation rule, particularly one based on subjective criteria, contributes to greater than trial-based continuation rates following listing (see table 5 below), and considered that the Stark 2017 retrospective chart review is likely to be subject to bias which tends to overestimate continuation beyond true effectiveness. The pre-PBAC response argued that the scenario for Botox in chronic migraine is different to the two examples provided as Botox patients are unlikely to overestimate their own response due to the mode of administration serving as a disincentive.

**Table 5: Differences between trial-based continuation rates and PBS continuation rates**

Morbidity and Treatment/s	RCT response rate	PBS continuation rate
Alzheimer disease treated by anti-dementia medicines	~30%	~60% <sup>a</sup>
Psoriatic arthritis treated by bDMARDs	Lower end of 36-77%, as the PBS continuation criteria is better aligned with ACR50 than ACR20	76-84% for same drug, 94% for any bDMARD <sup>b</sup>
Migraine treated by botulinum toxin	32.9% (predicted from trial data according to the Commentary)	74% <sup>c</sup>
		71.4% <sup>d</sup>

Sources: <sup>a</sup> Post-Market Review of PBS Anti-Dementia Medicines for Alzheimer Disease, 2012

<sup>b</sup> DUSC report: bDMARDs for psoriatic arthritis: utilisation analysis, October 2015

<sup>c</sup> Stark 2017 retrospective chart review

<sup>d</sup> DUSC report: Botulinum toxin type A for chronic migraine: 24 month predicted versus actual analysis, June 2017

6.8 There is also the risk of bias associated with the selection of the Stark 2017 retrospective chart review solely on the basis that it was an Australian study, resulting in the exclusion of all the other single arm studies with meaningfully differing conclusions without sufficient justification. The PSCR stated that the other real-world equivalent studies were not selected due to risk of bias as they were non-randomised trials. The ESC considered that the submission did not provide adequate justification for excluding the other studies. The PBAC considered that it was not unreasonable to use Australian data in preference to other sources. However, the

PBAC agreed with ESC that the exclusion of the other studies identified was not adequately justified.

### Comparative effectiveness

6.9 The table below provides a summary of results from the Stark 2017 retrospective chart review.

**Table 6: Summary of results from the Stark 2017 retrospective chart review**

Primary outcome	Results					
≥50% reduction in headache days per month after 2 BOTOX cycles	73.9% of patients (156/211)					
Additional outcomes	Baseline value		Change from baseline			
	N	Mean (SD)	26 weeks		60 weeks	
			N	Mean (SD)	N	Mean (SD)
Headache frequency						
Reduction in number of headache days per month	211	25.2 (5.3)	211	-14.7 (8.4)	137	-16.9 (9.0)
Reduction in number of severe headache days per month	111	12.0 (7.0)	105	-8.2 (6.8)	59	-8.5 (8.4)
Reduction in number of migraine days per month	197	15.3 (7.9)	189	-9.4 (7.6)	129	-10.0 (8.4)
Headache impact						
Reduction in HIT-6 score	100	68.2 (4.8)	80	-11.7 (9.8)	68	-11.8 (12.2)
Reduction in days of work or study missed per month	107	8.5 (9.5)	99	-5.0 (7.8)	50	-5.6 (7.7)
Concomitant medications						
Days acute pain medication was taken per month	183	19.2 (7.9)	167	-11.5 (7.6)	103	-12.7 (8.1)
	N	Baseline, n %	N	2 <sup>nd</sup> cycle %	N	Most recent cycle %
Proportion of patients taking simple analgesics	211	157, 74%	211	141, 67%	211	92, 44%
Proportion of patients taking triptans	211	136, 65%	211	134, 64%	211	93, 44%
Proportion of patients taking over-the-counter codeine	211	92, 44%	211	60, 28%	211	37, 18%
Proportion of patients taking opioids	211	49, 23%	211	28, 13%	211	19, 9%

Source: Section 2.6.5, p78-80 of the submission; 2a\_Non-Proportion Final Tables\_AP-BTX-CM-RWE-001.pdf; Table 4, p5 PSCR

6.10 As shown in the table above, the proportion of patients with a ≥ 50% reduction in headache days from baseline following two Botox treatment cycles was 73.9%.

6.11 In June 2017 DUSC conducted an analysis to compare the predicted versus actual utilisation of Botox for chronic migraine since its PBS listing in March 2014. The proportion of patients reporting a ≥ 50% reduction in headache days (73.9%) reported in the Stark 2017 retrospective chart review was similar to the 71.4% continuation rate calculated by DUSC. The proportion of patients with a ≥ 50% reduction in headache days who received Botox in the PREEMPT trials was 38.3% (pooled data for patients receiving ≥ 2 prior prophylactics). The submission proposed that the real-world data from Stark 2017 demonstrate that the effectiveness of BOTOX therapy in Australian clinical practice exceeds the effectiveness demonstrated in the PREEMPT trials.

6.12 The PBAC considered that the higher continuation rates observed in the Stark 2017 retrospective chart review could have been due to a range of explanations other than greater than expected efficacy:

- The study was uncontrolled and unblinded.

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- The study allowed the continued use of oral prophylactics (see also paragraph 6.14 below).
  - The response rate was calculated on the basis of headache diaries for only 48.8% of patients in the study, with the remaining 51.2% recorded by the physician. The reliability of such results, especially in the context of a subjective measure is unclear.
  - The PREEMPT trials showed a substantial placebo response in the BSC arms which has not been controlled for due to the single treatment arm structure of the Stark 2017 retrospective chart review. The ESC noted that this may also be compounded by the phenomenon where the perceived effect of a drug can sometimes be greater in the post-marketing phase and outside of a clinical trial setting, due to increased expectations, particularly for subjective measures.
  - A higher continuation rate compared to trial response rates has been observed for other PBS medicines where continued subsidy and prescribing is dependent upon a subjective continuation rule (see paragraph 6.7).
- 6.13 The submission suggested the Stark 2017 retrospective chart review population was similar to the PREEMPT (Phase 3 trial) populations, except for the inclusion of prior use of oral prophylactic treatments in the Stark 2017 treatment group. However, the ESC also noted that there were differences in chronic migraine duration and number of headache days (Table 7) and considered the impact of this on the observed efficacy in Stark 2017 compared to PREEMPT is unknown.

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**Table 7: Baseline demographics, clinical characteristics and treatments for Stark 2017 patients compared with PREEMPT (Phase 3 trial) patients**

Characteristic	Stark 2017 patients N=211	PREEMPT patients N=1384
Age, mean (SD) years	44.6 (12.5)	41.3 (10.5)
Duration of CM migraine, mean (SD) years	12.3 (12.0) n=144	19.2 (12.6)
Women	88.6%	86.4%
Baseline headache days/month, mean (SD)	25.3 (5.3)	19.9 (3.7)
Baseline migraine days/month, mean (SD)	15.3 (7.9) n=197	16.4 (5.8)
Baseline HIT-6 score, mean (SD)	68.2 (4.8) n=100	65.5 (4.2)
Patients with severe ( $\geq 60$ ) HIT-6 score	98.0% n=100	93.1%
Previously used $\geq$ headache prophylactics	100%	63.5%
Prior use of amitriptyline	72.0%	24.3%
Prior use of topiramate	71.6%	41.0%
Prior use of propranolol	67.8%	20.2%
Continued oral headache prophylactics	66.4%	0%
Acute medication overuse at baseline <sup>a</sup>	61.1%	65.5%
Concomitant use of simple analgesics	74.4%	67.3%
Concomitant use of triptans	64.5%	63.3%
Concomitant use of prescribed opioids	23.2%	8.1% <sup>b</sup>

Abbreviations: CM = chronic migraine; HIT-6 = Headache Impact Test; SD = standard deviation

<sup>a</sup> Defined as: PBS = patient's records note them to be on a management plan for medication overuse; PREEMPT = simple analgesics  $\geq 15$  days/month, triptans  $\geq 10$  days/month or opioids  $\geq 10$  days/month

<sup>b</sup> Additionally 55.4% used 'Combination Analgesics' and 58.1% used 'Combined Categories'

Source: Table 2-12, p84 of the submission

- 6.14 Table 7 indicates that 66.4% of patients assessed at baseline in the Stark 2017 retrospective chart review continued oral headache prophylactics. The PBAC considered it likely that the continued use of oral prophylactics in the Stark 2017 population may have contributed to the greater proportion of patients achieving  $\geq 50\%$  reduction in headache days compared to the PREEMPT trial where continuation of oral prophylactic medications was not allowed.
- 6.15 The results of the 13 additional real-world studies showed that in most of the studies the proportion of patients with  $\geq 50\%$  reduction in headache days was less than 40%. This differed considerably from the results of Stark 2017, with a response rate of 73.9%. The submission claimed that several of the study response rates are higher than the corresponding results from PREEMPT. There were a number of studies with response rates similar to the PREEMPT rates (39.5% in COMPEL, 40.0% in FORWARD). The PSCR identified three studies in addition to Stark 2017 that had shown response rates over 40%: Dominguez 2016: 70.2%; Santoro: 66.0%; and Rothrock: 48.8%. However, the ESC noted the Santoro 2017 results were based on a small subgroup of the Santoro 2017 study; and at the same follow-up point as Stark 2017, the Rothrock 2016 study had a 37% response rate.

- 6.16 The submission cited results from 5 additional studies that reported response rates greater than those observed in PREEMPT: Demiryurek 2016 (Turkey; 88.3%), Cernuda-Morollon *et. al.* 2015 (Spain; 81.8%), Vikelis 2016 (Greece; 80.2%), Pedraza 2015 (Spain; 69.2%), and Kollewe 2016 (Germany; 63.0%). The submission had excluded these studies from further review due to their population size being less than 200. An additional study meeting these criteria was presented in the PSCR Cesaretti 2015 (Italy; 50.0%). The ESC noted that, whilst the rates of continuation were also higher in a number of the other real-world evidence identified in the submission compared to PREEMPT, Stark 2017 remained an outlier with estimates at the higher end of the spectrum. The pre-PBAC response disagreed with Stark 2017 being characterised as an outlier and argued that there are at least ten real-world studies reporting  $\geq 50\%$  in headache days per month higher than the 24 week results seen in PREEMPT. However, the PBAC agreed with ESC that the results of the Stark 2017 retrospective chart review appear at the high end of the range and was concerned that there was no exploration of the variability evident in the real-world studies presented. Given that the submission provided inadequate justification for the exclusion of these studies from the primary results analysis, and given the variability in results noted above, the reliance on Stark 2017 data was problematic.
- 6.17 The results for all additional outcomes (headache frequency, headache impact, use of concomitant medications) in the Stark 2017 retrospective chart review should be interpreted with caution. Reduction in headache, severe headache and migraine days per month are difficult to quantify with no baseline value provided. There were substantially different patient numbers at each assessment point compared to baseline which makes it difficult to interpret the magnitude of the decrease. The PSCR provided an updated summary of results table with patient numbers for headache and migraine rates, and use of concomitant medicines, at baseline, after two treatment cycles and at the end of the trial. These have been included in Table 6 above.
- 6.18 For reference, the key results of the PREEMPT trials (change from baseline in number of headache days), as presented in the July 2013 resubmission, are summarised below.

**Table 8: Pooled results for the number of headache days in the PREEMPT trials as presented in the July 2013 resubmission**

Population	Botox Mean (SD)			BSC Mean (SD)			Mean difference (95% CI)
	N	Baseline	Change	N	Baseline	Change	
<b>Number of headache days</b>							
ITT	688	19.9 (3.7)	-8.4 (6.6)	696	19.8 (3.7)	-6.6 (6.7)	<b>-1.8 (-2.52, -1.13)</b>
≥2 prior prophylactics	313	20.1 (3.7)	-7.7 (6.4)	325	20.0 (3.8)	-5.1 (6.4)	<b>-2.7 (-3.67, -1.68)</b>
≥3 prior prophylactics	231	20.0 (3.5)	-7.4 (6.6)	248	20.2 (3.9)	-4.7 (6.4)	<b>-2.7 (-3.81, -1.48)</b>

Source: Table 2-5, p51 of the submission.

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

6.19 On consideration of this PREEMPT evidence in the July 2013 resubmission, the PBAC stated that in July 2012 it was accepted that a change of two to three headache days as shown in the PREEMPT trial was a clinically meaningful outcome (Botulinum Toxin Type A PBAC PSD, July 2013).

6.20 The results from the PREEMPT trials for proportion of patients with ≥ 50% reduction in headache days (a secondary outcome for the trials), which were provided in the July 2012 resubmission, are summarised in the table below.

**Table 9: Proportion of patients with ≥ 50% reduction in headache days per month at week 24 in the PREEMPT trials**

Population	Botox n/N (%)	BSC n/N (%)	RR (95%CI)	RD (95%CI)
<b>≥50% reduction in headache days</b>				
ITT	286/685 (41.8%)	222/693 (32.0%)	<b>1.30 (1.13, 1.50)</b>	<b>0.097 (0.05, 0.15)</b>
≥2 prior prophylactics	120/313 (38.3%)	82/324 (25.3%)	<b>1.51 (1.20, 1.91)</b>	<b>0.130 (0.06, 0.20)</b>
≥3 prior prophylactics	85/231 (36.8%)	57/247 (23.1%)	<b>1.59 (1.20, 2.12)</b>	<b>0.137 (0.06, 0.22)</b>

Source: Table 2-7, p53 of the submission.

BSC=best supportive care; CI=confidence interval; ITT=intention to treat; RD=risk difference; RR=relative risk; **bold**=statistically significant

### **Comparative harms**

6.21 There were no adverse event data reported in the Stark 2017 poster. The poster stated that the case report form requested information on adverse events but none were reported. Neither the submission or the Stark 2017 poster provided any discussion of whether this meant there were actually no adverse events, or if there were events but they had not been reported. The absence of adverse event data from the retrospective chart review limits its informativeness.

6.22 The PREEMPT trials demonstrated statistically significant differences between Botox and BSC for the following AEs: 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%) (Botulinum Toxin Type A PBAC PSD, July 2013). The submission indicated that the safety results in the 13 additional real-world studies were consistent with those reported in the PREEMPT trials and with the known safety profile of Botox. This was reasonable.

## **Benefits/harms**

6.23

Accordingly, a benefits/harms table has not been presented.

## **Clinical claim**

- 6.24 The submission stated that in the PBS population treated with Botox for chronic migraine (Stark 2017 retrospective chart review), patients achieved better clinical outcomes than those achieved by patients in the pivotal trials (PREEMPT trials). The submission used this claim to support its proposed revision to the RSA. The PBAC considered that this claim was inadequately supported by the evidence provided.
- 6.25 While the proportion of patients in the Stark 2017 retrospective chart review who achieved a  $\geq 50\%$  reduction in headache days per month (73.9%) was greater than that observed in the clinical trials, as noted above it remained possible that this outcome was influenced by continued use of oral prophylactic medications in the Stark 2017 cohort as well as the subjective nature of outcome assessment. Results from the Stark 2017 retrospective chart review should be interpreted with caution given missing data.
- 6.26 The PBAC considered that while the Stark 2017 retrospective chart review demonstrated higher continuation rates than the PREEMPT trial, a higher rate of continuation could potentially be attributed to other factors not directly associated with better than expected efficacy (open-label design, considerable placebo effect, influence of a continuation rule). The PBAC also considered that the outcomes assessments by headache diary or physician assessment were subjective measures. In the context of these uncertainties and the lack of a control arm, the PBAC concluded that the evidence presented did not provide evidence of greater efficacy than observed in the PREEMPT trial.

## **Economic analysis**

- 6.27 The submission updated the modelled economic evaluation presented in the July 2013 resubmission, with data from the Stark 2017 retrospective chart review replacing the PREEMPT data in the Botox arm of the model only. The table below outlines the key components of the economic evaluation.

**Table 10: Summary of model structure and rationale**

<b>Component</b>	<b>Summary</b>
Time horizon	5 years in the model base case versus 24 weeks in the trials and non-randomised study.
Outcomes	QALYs
Methods used to generate results	Markov cohort analysis
Health states	6 health states defined by the number of headache days per 28 days.
Cycle length	12 weeks to correspond to Botox re-injection cycle.
Transition probabilities	Stark 2017 retrospective chart review for Botox and PREEMPT, a randomised controlled trial, for BSC.

Source: Table 3-1, p97 of the submission.

- 6.28 The submission stated that the Stark 2017 data provided an opportunity to re-populate the already presented and evaluated economic model with real-world PBS data, which allows Botox’s cost-effectiveness on the PBS to be presented to the PBAC.
- 6.29 The PBAC has previously identified the following issues with the economic model: the transition probabilities; the utility values; the extrapolation of the incremental treatment effect of Botox 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 IBMS/BIS as the source of resource utilisation costs. Detail on these issues, which remain, are as follows:
- Transition probabilities: were not sufficiently robust as they were derived from post-hoc sub-group analyses (of PREEMPT) that were not sufficiently powered to assess the transition between six separate health states (Section 12, p6 November 2011 PSD).
  - Utility values: the IBMS/BIS may overestimate the incremental benefit associated with moving between the health states (Section 12, p6 November 2011 PSD), and the utility values in the IBMS/BIS study were not specific to botulinum toxin treatment and that the study included few Australian patients (Section 10, p5 July 2013 PSD).
  - Extrapolation of treatment effect: all previous models had a high extrapolation to evidence ratio, whereas any continued effect of botulinum toxin type A is highly uncertain (Section 12, p6 November 2011 PSD; and July 2012 PSD; Section 10, p6 July 2013 PSD).
  - Use of IBMS/BIS as source of resource utilisation costs: the IBMS/BIS study included few Australian patients and that health resource utilisation from this study may not accurately represent management of chronic migraine in Australia (Section 10, p5 July 2013 PSD).
- 6.30 The PSCR argued that the model structure and assumptions were considered acceptable in 2013, despite these concerns. The PBAC was of the view that, while it had accepted the model was sufficiently robust to support a recommendation at the time, this did not imply that the model was sufficiently robust for a reanalysis of effectiveness using single-arm data.

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- 6.31 The PSCR indicated that since the submission was put forward, EQ-5D utility data from the REPOSE study had become available. The PSCR claimed that these data showed that the utility data from the IBMS used in the model was potentially conservative, as the utility value between best and worst health states was 0.33 in the base case model, but could be 0.42 using REPOSE. The ESC noted that the UK EQ-5D algorithm was generally considered to have a broader spread of scores than most other existing algorithms. Moving from the UK algorithm would likely increase the ICER but the magnitude is difficult to quantify. The ESC considered that this was relevant given that the incremental benefit in QALYs as a result of a reduction in migraine days is only driven through improvements in quality of life and that the use of the Australian scoring algorithm would have been more relevant.
- 6.32 Overshadowing these identified issues with the model is the submission’s use of single arm data at a high risk of bias from the Stark 2017 retrospective chart review along with RCT-based data from the PREEMPT trials in the BSC comparator arm. As the PBAC had concluded the submission’s clinical claim was inadequately supported by the evidence provided, the PBAC did not accept that the approach taken to update the economic model with the results from the Stark 2017 retrospective chart review was valid.
- 6.33 The continued use of BSC data from PREEMPT did not account for the possibility that there may have been changes in what constitutes BSC as well as its costs and benefits since the PREEMPT trial (2006 to 2008). The PSCR claimed that BSC has not changed since its recommendation in July 2013, with no new drug approvals nor PBS listings for chronic migraine medications in Australia. The ESC noted that BSC included aspects of management other than drugs, and considered that while changes in BSC could have affected the baseline and response rate, the direction and magnitude of this is unknown.
- 6.34 The results of the economic evaluation presented in the submission are provided in the table below.

**Table 11: Results of the economic evaluation**

	<b>Botox</b>	<b>BSC</b>	<b>Increment</b>
<b>March 2018 - model updated with Stark 2017 data</b>			
Costs	\$ [REDACTED]	\$8,866	\$ [REDACTED]
QALYs	2.5404	2.2474	0.2930
<b>Incremental cost/extra QALY gained</b>			<b>\$ [REDACTED]</b>
<b>July 2013 model</b>			
Costs	\$ [REDACTED]	\$8,709	\$ [REDACTED]
QALYs	2.4836	2.3191	0.1645
<b>Incremental cost/extra QALY gained</b>			<b>\$ [REDACTED]</b>

Source: Table 3-10 and Table 3-11, p108 of the submission.

BSC=best supportive care

- 6.35 The submission presented a revised ICER of \$15,000/QALY - \$45,000/QALY gained (Table 11). The submission maintained the same ex-manufacturer cost for Botox as used in the July 2013 resubmission and did not apply the F1 5% statutory price reduction of April 2016. Use of the ex-manufacturer price of Botox based on the F1

5% statutory price reduction of \$ [REDACTED] lowered the ICER, as would be anticipated, by about \$ [REDACTED] to \$15,000/QALY - \$45,000/QALY. The PBAC noted the revised ICER of \$15,000/QALY - \$45,000/QALY and the effect of the application of the 5% statutory reduction. However, due to concerns regarding the model and its inputs the PBAC did not consider that the revised ICER provides adequate justification for improved or similar cost effectiveness.

- 6.36 The submission did not present any sensitivity analyses of the updated economic evaluation although the submission identified the revised base case as a sensitivity analysis of the July 2013 model. Three new sensitivity analyses (SA) were presented in the PSCR:
- SA1 = no stopping rule: this minimally reduced the ICER to \$15,000/QALY - \$45,000/QALY from \$15,000/QALY - \$45,000/QALY the 2013 base case;
  - SA2 = application of REPOSE utility data, described above in 6.29: this reduced the ICER to less than \$15,000/QALY from \$15,000/QALY - \$45,000/QALY; and
  - SA3 = replacing the BSC PREEMPT placebo arm with the baseline results (removing placebo effect): this reduced the ICER to less than \$15,000/QALY from \$15,000/QALY - \$45,000/QALY.
- 6.37 The ESC considered that the main issue was the difference in characteristics between subjects in the PREEMPT trial and the Stark 2017 study at baseline. As noted above, the PSCR provided Sensitivity Analysis 3 whereby the placebo effects in the BSC arm were removed, which considerably reduced the ICER. The ESC considered that this was inappropriate, and that it would be more informative to adjust the values used in the BSC arm to account for differences in baseline between the PREEMPT trials and the Stark 2017 study, but that the placebo effect observed in PREEMPT should still be applied to the BSC arm in the model, as its exclusion is unjustified, particularly in light of the considerable placebo effect observed.
- 6.38 The PBAC concluded that the comparison provided in the current updated model (Stark 2017 data for Botox and PREEMPT data for BSC) did not allow for an accurate estimate of the cost-effectiveness of Botox in the treatment of chronic migraine.

### **Drug cost/patient/course**

- 6.39 The cost of Botox therapy per injection is \$ [REDACTED]. This was based on the ex-manufacturer cost of \$ [REDACTED] and assumed usage of 1.9 vials per administration plus private hospital mark-up (\$ [REDACTED] per vial) and dispensing fee (\$ [REDACTED]). The cost applied in the July 2013 model (\$ [REDACTED]) assumed 2 vials and did not include mark-ups or dispensing fees as these were not part of the Botox price at the time. The submission has maintained the same ex-manufacturer cost for Botox as used in the July 2013 resubmission and has not applied the F1 5% statutory price reduction of April 2016. When that price reduction is applied the cost of Botox therapy per injection becomes \$ [REDACTED].

**Estimated PBS usage & financial implications**

6.40 This submission was not considered by DUSC. However in June 2017 DUSC released a 24-month predicted versus actual analysis of the use of Botox for chronic migraine. Key findings were that the number of treated patients was substantially higher than predicted and MBS services for administration were substantially greater than expected. Analysis by DUSC found that the continuation rate following two Botox treatments was 71.4%, which was more than double that predicted from trial data (32.9%). DUSC considered that “the difference between the trial and real-world continuation rates may be the subjective nature of the assessment” (p27 DUSC report: Botulinum toxin type A for chronic migraine: 24 month predicted versus actual analysis, June 2017). DUSC also noted that if the sponsor were to request a change to the RSA, a submission to the PBAC would be required.

6.41 The submission requested a revision to the current Botox RSA for chronic migraine, where there are currently [REDACTED].

[REDACTED]

The PBAC considered that this assumption was not adequately supported by the data provided.

6.42 To support the revised cap structure the submission formulated revised financial estimates based on the Stark 2017 retrospective chart review. However, the submission did not apply these estimates to the requested [REDACTED] and instead based the [REDACTED] on [REDACTED]. Following are key points regarding the revised estimates presented in the submission, with numbers provided in the following table.

- Current estimates: The current financial estimates were based on diagnosed patients who have trialled 3 prophylactic agents and are seeing a neurologist who can inject Botox. A continuation rate of 73.9% from Stark 2017 was applied, and the number of injections per year per patient was sourced from Stark 2017.

- Requested new cap: [REDACTED]

[REDACTED]

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- Rebate above the cap: [REDACTED]
- [REDACTED]: [REDACTED]. This is inappropriate as the net financial impact of a change to a listing should be based on a comparison of actual utilisation in the current situation to the expected utilisation in the proposed scenario, not cap numbers. Given the rebate over [REDACTED], use beyond this cap still incurs a cost to government.

Table 12: Current estimates and proposed new cap

	Year 1 2018	Year 2 2019	Year 3 2020	Year 4 2021	Year 5 2022	Year 6 2023
<b>Current estimates based on Stark 2017</b>						
Eligible population	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Market uptake	48.7%	51.1%	54.8%	58.0%	60.8%	63.2%
Patients initiating treatment	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Total vial numbers	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Net cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
<b>July 2013 resubmission estimates – extended to 2023</b>						
Eligible population	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Market uptake	48.7%	51.1%	54.8%	58.0%	60.8%	63.2%
Patients initiating treatment	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Total vial numbers	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Net cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
<b>Proposed cap - based on estimates from the July 2013 resubmission</b>						
Sourced from net cost to PBS/RPBS July 2013	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Rebate % above cap	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
RSA amount	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Cap 2 (budgeted amount)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
<b>Net impact (proposed new cap minus budgeted amount)</b>						
Net impact	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Table 4-20, p131 of the submission.

The redacted table shows that at Year 6, the estimated number of patients initiating treatment would be less than 10,000 per year, and the net cost to the PBS would be \$30 – 60 million per year.

6.43 Over 6 years the estimated net cost to the PBS/RPBS based on the Stark 2017 estimates was more than \$100 million. The estimated net impact of the difference between the proposed new cap and the RSA amount [REDACTED].

6.44 The PBAC considered that there are a number of concerns with the current estimates [REDACTED]:

- The  $\geq 50\%$  response rate observed in Stark 2017 retrospective chart review (73.9%) may have been influenced by continued use of oral prophylactic medications in the Stark 2017 cohort as well as the subjective nature of outcome

assessment. The Stark 2017 results were on the high end of the range reported for other real-world studies with the variability evident across these studies not explored. Further, application of this data to the economic model without any corresponding changes in the comparator BSC arm limited the applicability of the cost-effectiveness results. Overall, the Stark 2017 data was not strongly supported as a source of financial estimates.

- While the submission formulated estimates based on the Stark 2017 data, the submission did not apply these estimates [REDACTED] and instead used estimates based on [REDACTED]. This created an inconsistency between the financial estimates and the cap values and it would seem appropriate to base the cap values on the same data sources as the estimated usage and cost values. The PSCR stated that data derived from real-world use can be imperfect, thus the sponsor [REDACTED]. The PBAC considered that this inconsistency complicated the interpretation of the financial estimates and the cap values.
- The use of the ex-manufacturer price for Botox in the financial estimates, the failure to include dispensing fees and mark-ups, patient copayments and the F1 5% statutory price reduction mean that the estimated costs were not accurate. When estimated net costs using the F1 5% statutory price reduction were applied, which decreased estimated net costs to more than \$100 million over the first 6 years following [REDACTED], the estimated net impact [REDACTED]. The PSCR indicated the price was left unchanged “for consistency (and ease of comparison) with the 2013 model”, and did not incorporate the F1 price cut, which was believed [REDACTED]. The ESC considered that this was inappropriate.
- The submission has not accounted for patient copayments. The PSCR noted that this would slightly overestimate the net cost to Government, “because the average patient co-payment (\$ [REDACTED]) will marginally exceed the average fees and mark-ups for a standard script for 2 vials (\$ [REDACTED]). The difference is less than \$ [REDACTED] per vial (\$ [REDACTED] per script)”. The ESC was of the view that the sponsor should use the most accurate and up-to-date data available in its financial estimates.
- The submission used the cap numbers rather than current utilisation and costs to assess the net impact of the proposed change to the RSA; this is inappropriate and limits the usefulness of these estimates.

6.45 The submission did not provide any sensitivity analyses of its revised financial estimates based on Stark 2017 data nor of the July 2013 estimates [REDACTED]. It would be most appropriate to delay sensitivity analyses until drug

costs have been corrected, in terms of updating the ex-manufacturer cost of Botox to DPMQ and applying the F1 5% statutory price reduction and patient copayments in the financial estimates. Due to a range of other issues with the estimates, these steps were not taken during the evaluation.

- 6.46 The ESC noted that the DUSC data showed both higher initiation and continuation rates than accepted by the PBAC in July 2013. At the time of recommending the listing, the PBAC was of the view that there was considerable uncertainty in the size of the population that would be eligible for Botox treatment. The PBAC considered that the submission had not presented any data to support whether the higher than expected initiation rates could be attributed to appropriate use. The PBAC noted that the proposed continuation rates were based on the assumption that all continuation was appropriate, which the PBAC considered was not adequately supported by the data presented in the submission.

### ***Quality Use of Medicines***

- 6.47 The submission stated that quality use of medicine (QUM) activities had been described in the July 2013 resubmission. In the July 2013 resubmission, activities to support QUM were described as well as post-marketing studies and use of patient diaries. The submission added that the sponsor continues to monitor any adverse events associated with Botox use for chronic migraine as part of the TGA-approved risk management plan.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **7 PBAC outcome**

- 7.1 The PBAC rejected the request to revise the Risk Sharing Arrangement (RSA) relevant to the use of Botox under its PBS listing for the treatment of chronic migraine. The PBAC considered that the claim made by the submission that the RSA should be revised as the greater than predicted use of Botox was due to greater than expected efficacy, and hence was cost-effective, was not adequately supported by the evidence presented.
- 7.2 The PBAC noted that the DUSC 24-month predicted versus actual analysis of the use of Botox showed both higher initiation and continuation rates than predicted. The PBAC considered that the higher than estimated use of Botox in chronic migraine was not unexpected, and recalled that the recommendation for the original RSA was to address this, and the uncertainty that the cost-effectiveness would be reflected in practice.
- 7.3 The PBAC noted that the Stark 2017 retrospective chart review served as the key evidentiary basis of the requested RSA revision. The PBAC considered that the study had a high risk of bias as it was uncontrolled and unblinded, with less than half the participants utilising a headache diary in the assessment of the primary outcome. The PBAC also noted that there is some evidence that a PBS continuation rule,

particularly one based on subjective criteria, may contribute to greater than trial-based continuation rates and considered that the Stark 2017 study is likely to be subject to such a bias.

- 7.4 The PBAC noted that the submission claimed the results of the Stark 2017 retrospective review indicated a higher proportion of patients are satisfying continuation criteria ( $\geq 50\%$  reduction in the number of headache days per month) than observed in the PREEMPT trials (73.9% versus 38.3% respectively). The PBAC noted that the continuation rate reported in the Stark 2017 study was similar to the 71.4% continuation rate calculated by DUSC.
- 7.5 The PBAC considered that, while the Stark 2017 retrospective chart review demonstrated higher continuation rates than the PREEMPT trial, the higher rate of continuation could potentially be attributed to other factors not directly associated with better than expected efficacy (open-label design, considerable placebo effect, continued use of oral prophylactic treatments, influence of a continuation rule). The PBAC also considered that the outcomes assessments by headache diary or physician assessment were subjective measures. The PBAC concluded that the Stark 2017 study likely over-estimated the incremental response rate for Botox use in chronic migraine.
- 7.6 The PBAC noted that the response rates reported in the other real-world studies included in the submission had variable results, with results of the Stark 2017 study appearing on the high end of the range. The PBAC noted that the Stark 2017 study was not the only outlier; however, the Committee was concerned that there was no exploration of the variability of response rates evident in the real-world studies presented, nor was there an adequate justification for exclusion of these studies.
- 7.7 In the context of the uncertainty regarding the results of the Stark 2017 retrospective chart review and the nature and variability of the remaining real-world studies presented in the submission, the PBAC concluded that the evidence presented did not provide a reliable basis for a claim of greater efficacy of the use of Botox in chronic migraine than observed in the PREEMPT trials. The PBAC reiterated that the results of the PREEMPT trials provide the most reliable measure of the proportion of patients likely to be considered full responders to Botox.
- 7.8 The PBAC noted that the submission did not address previously identified issues with the economic model. In addition, the PBAC considered that the continued use of BSC data from the PREEMPT trials did not account for the possibility that there may have been changes in what constitutes BSC as well as its costs and benefits since the trial was conducted. However, the PBAC considered that the submission's use of single arm data at a high risk of bias from the Stark 2017 retrospective chart review along with RCT-based data from the PREEMPT trials in the BSC comparator arm overshadowed the identified issues with the model. As the PBAC considered the submission's clinical claim was inadequately supported by the evidence provided, the Committee did not accept that the approach taken to update the economic

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model with the results from the Stark 2017 retrospective chart review was valid.

- 7.9 Culminating from this, the PBAC did not accept that the data provided in the current updated model provided any greater certainty that the increased utilisation is cost effective or that the pattern of use is any more cost effective than originally anticipated. The PBAC therefore concluded that there was an inadequate justification for the requested changes in the RSA [REDACTED].
- 7.10 The PBAC noted that, while the submission formulated estimates based on the Stark 2017 data, the submission did not apply these estimates to the proposed [REDACTED] and instead used estimates based on [REDACTED]. The PBAC considered this inconsistency complicated the interpretation of the financial estimates and the [REDACTED].
- 7.11 The PBAC noted that the submission proposed a [REDACTED]. There was negligible rationale for the [REDACTED] used in the context of the new RSA proposal [REDACTED]. The PBAC considered that this assumption was not adequately supported by the data provided.
- 7.12 The PBAC noted the submission's claim that some of the increased utilisation may be derived from more of the eligible population achieving full response and is therefore being used within the intention of the restriction, thus some modification of the RSA arrangements may be reasonable; however the evidence provided in this submission was not considered a reliable basis for the proposed changes to the current risk sharing arrangement. If any changes in the structure of the RSA were to be implemented, the PBAC advised that these should have no net financial consequence for the PBS.
- 7.13 The PBAC considered that its original concern in the context of the prior July 2013 submission of usage beyond the intention of the restriction remained.
- 7.14 The PBAC did not support the submission's request to increase the level of authority to a written authority. The PBAC considered that this request was contrary to the arguments put forward in the submission that all current use was within the intent of the original listing and cost-effective. In this case, the sponsor's request would increase administrative burden on the prescribers, with no clinical justification.
- 7.15 The PBAC noted that this submission is not eligible for an Independent Review as it was a request to modify an existing listing arrangement.

**Outcome:**  
Rejected

## **8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

## **9 Sponsor's Comment**

The sponsor had no comment.