5.7 INCOBOTULINUMTOXIN A, powder for solution for injection, 100LD$_{50}$ units, Xeomin®, Merz Pharmaceuticals GmbH.

1 Purpose of Application

1.1 To request a Section 100 (Botulinum Toxin Program) listing for incobotulinumtoxinA (Xeomin®) to treat cervical dystonia, blepharospasm and post-stroke upper limb spasticity.

2 Requested listing

2.1 The submission sought the following listing:

Name, Restriction, Manner of administration and form	Max. Qty packs	Max. Qty units	Proprietary Name and Manufacturer	
INCOBOTULINUMTOXINA				
Purified neurotoxin free from complexing proteins, powder for solution for injection, 1 x 100LD$_{50}$ units	1	1	XEOMIN®	Merz Pharmaceuticals GmbH
The date of the stroke must be provided.				
Contraindications to treatment include established severe contracture and known sensitivity to botulinum neurotoxin.				

2.2 Listing was sought on a cost-minimisation basis with onabotulinumtoxinA (Botox®) as the comparator.

2.3 The requested listing for the treatment of upper limb spasticity limits a maximum number of treatments to 4, without defining the word "treatments". The PBS restrictions for the other two forms of botulinum toxin type A, Botox® and Dysport®, specify that the total number of "treatments" should include treatment with either Botox® or Dysport®. The PBAC may wish to consider whether the relevant eligibility criterion in the requested Xeomin® restriction should be revised to read "Maximum number of treatments to be authorised is 4 (total Xeomin®, Botox® and Dysport®) per upper limb per lifetime". A similar change is suggested to the current listings for Botox® and Dysport®, if the PBAC recommends the listing of Xeomin®. The ESC agreed this was reasonable and remodelling of current restrictions for Botox® and Dysport® would be necessary if incobotulinum toxin A is accepted by the PBAC.

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

3 Background

3.1 IncobotulinumtoxinA was TGA registered on 21 March 2014 for the treatment of: Cervical dystonia in adults; Blepharospasm in adults; Post-stroke spasticity of the upper limb in adults; Glabellar frown lines in adults.

3.2 IncobotulinumtoxinA had not been previously considered by the PBAC.

4 Clinical place for the proposed therapy

4.1 Cervical dystonia is characterised by involuntary contractions of specific muscles leading to abnormal movements of the head and/or unintentional adoption of sustained and frequently painful postures of the head, neck and shoulders. In patients with cervical dystonia, botulinum toxin A is usually used either as monotherapy or as an adjunct to standard care, *eg* physical therapy and oral medications.

4.2 Blepharospasm is a focal dystonia characterised by involuntary contraction of orbicularis oculi, causing involuntary closure of the eyes. Botulinum toxin A is the only effective treatment for blepharospasm.

4.3 For patients who have upper limb spasticity following a stroke, physical rehabilitation ± oral spasticity agents is the first-line therapy. Patients with sustained moderate to severe spasticity may be treated with botulinum toxin in conjunction with rehabilitation.

4.4 There are currently two botulinum toxin preparations listed on the PBS: onabotulinum A (Botox®) and abotulinumtoxin A (Dysport®).

4.5 Xeomin® offers patients an alternative form of botulinum toxin A for treatment of cervical dystonia, blepharospasm and post-stroke spasticity of the upper limb. The listing of Xeomin® for each of the three indications proposed in the submission will not alter the current clinical management of patients in Australia.

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

5 Comparator

5.1 The submission nominated Botox® as the comparator. The unit of Xeomin® corresponds to the median lethal dose (LD50) in mice when the reconstituted product is injected intraperitoneally into mice under defined conditions. The potencies of Xeomin® and other botulinum toxin A preparations, including Botox® and Dysport®, are determined via different assay methods. Units of biological activity of Xeomin® should not be directly compared to units of any other botulinum toxin activity, unless the dose relativity between the two botulinum toxin A preparations has been accepted by the PBAC.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The submission presented two head-to-head randomised trials comparing efficacy and safety of XEOMIN® to that of BOTOX® in the treatment of adult patients with

cervical dystonia (Trial 0013) or blepharospasm (Trial 0003). The submission also presented one double-blind randomised trial (Trial 0410) for an indirect comparison between XEOMIN® and BOTOX® using placebo as the common reference in adult patients with post-stroke spasticity of the upper limb.

6.4 Trials and associated reports presented in the submission are shown in the table below.

Trial ID	Protocol title/ Publication title	Publication citation
Xeomin® *versus* Botox®		
Cervical Dystonia		
Trial 0013	Integrated clinical and statistical study report MRZ 60201-0013: Safety and efficacy of NT 201 (highly purified botulinum neurotoxin A) compared to Botox® (purified botulinum neurotoxin A-complex) in cervical dystonia. Benecke R, Jost WH, Kanovsky P, Ruzicka E, Comes G, Grafe S. A new botulinum toxin type A free of complexing proteins for treatment of cervical dystonia.	January 2003 *Neurology* 2005; 64(11):1949-51
Blepharospasm		
Trial 0003	Integrated clinical and statistical study report MRZ 60201-0003: Safety and efficacy of NT 201 (highly purified botulinum neurotoxin A) compared to Botox® (purified botulinum neurotoxin A-complex) in blepharospasm. Roggenkamper P, Jost WH, Bihari K, Comes G, Grafe S. Efficacy and safety of a new botulinum toxin Type A free of complexing proteins in the treatment of blepharospasm. Jankovic J. Clinical efficacy and tolerability of Xeomin® (registered trademark) in the treatment of blepharospasm.	January 2003 *Journal of Neural Transmission* 2006; 113(3):303-12. *European Journal of Neurology 2009; 16(SUPPL. 2):14-8.*
Xeomin® *versus* placebo		
Post-stroke spasticity of the upper limb		
Trial 0410	Integrated clinical and statistical study report MRZ 60201-0410: Prospective, double-blind, placebo-controlled, randomised, multi-center trial with an open-label extension period to investigate the efficacy and safety of NT 201 in the treatment of post-stroke spasticity of the upper limb Kanovsky P, Slawek J, Denes Z, Platz T, Sassin I, Comes G, et al. Efficacy and safety of botulinum neurotoxin NT 201 in post-stroke upper limb spasticity. Kanovsky P, Sassin I, Comes G, Grafe S. Efficacy and safety of NT 201 (Xeomin®) in the upper limb post-stroke spasticity in a double-blind placebo-controlled randomised multi-center trial. Prospective, Double-blind, Placebo-controlled, Randomised, Multi-center Trial With an Open-label Extension Period to Investigate the Efficacy and Safety of incobotulinumtoxin-A (Xeomin®) in the Treatment of Post-stroke Spasticity of the Upper Limb. NCT00432666	March 2009 *Clinical Neuropharmacology* 2009; 32(5):259-65. *Movement Disorders* 2008; 23:S377. November 2010

Source: Table 13, p56 of the main submission

6.5 Key features of the trials are shown in the table below.

Trial	N	Design/ duration	Risk of bias[a]	Patient population	Key outcomes
Cervical dystonia (XEOMIN® *vs* BOTOX®)					
Trial 0013	463	R, DB, MC 16 weeks	Low	Patients with cervical dystonia who had prior stable response to previous BOTOX® treatment	Primary: change from baseline in the TWSTRS – severity score at the control visit (28±7 days after treatment). Secondary: • change from baseline in the TWSTRS – severity score at the final visit[b] • time to onset of treatment effect

					• time to waning of treatment effect • duration of treatment effect
Blepharospasm (XEOMIN® *vs* BOTOX®)					
Trial 0003	303	R, DB, MC 16 weeks	Low	Patients with blepharospasm who had stable response to previous BOTOX® treatment	Primary: the change from baseline in the JRS sum score at the control visit (Day 21±1) Secondary: • change from baseline in the JRS sum score at the final visit[c] • change from baseline in the mean total score of BSDI at the control visit • change from baseline in the mean total score of BSDI at the final visit[c]
Post-stroke upper limb spasticity (XEOMIN® *vs* placebo, indirectly compared with the data presented in the BOTOX® PSD July 2008)					
Trial 0410	148	R, DB, MC 12-20 weeks[d]		Patients with upper limb spasticity following a stroke, treatment naïve or treatment experienced	Primary: ratio of proportions of responders (≥1-point decrease in AS scores) between treatment groups at Week 4 as determined for wrist flexors Secondary: • response rate at Week 4 for wrist flexors (≥2-point decrease in AS scores) • response rate at Weeks 2, 4, 8, 12 and the final visit[d] for each treated clinical pattern (≥1-point decrease in AS scores) • changes in AS scores from baseline to final visit[d] for each therapeutic domain
Low risk of bias in Trial 0410 but, due to use of this trial in an indirect comparison that is affected by poor trial exchangeability, there is a high risk of bias in the results					

R = randomised; DB = double blind; MC = multi-centre; JRS = Jankovic Rating Scale; BSDI = Blepharospasm Disability Index; PSD = Public Summary Document; AS = Ashworth Scale; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale.
[a] For the risk of bias in the trial included in the indirect comparison, see the comments *in italics* in the row below the trial.
[b] The final visit was defined as the time at which the TWSTRS severity score has reached at least 80% of the baseline value, or at the latest 112 days after injection.
[c] The final visit occurred 109-112 days after the injection or whenever the patients felt a need for a new injection session of botulinum toxin A.
[d] The final visit occurred between Week 12 and Week 20, depending on the time point when the patient and the investigator felt a need for a new injection
Source: compiled during the evaluation

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

Comparative effectiveness

Cervical dystonia

6.6 The results for the primary outcome, change from baseline in TWSTRS-Severity score to the control visit (28±7 days after treatment) are summarised in the table below.

Change from baseline to control visit in TWSTRS-Severity score (final ANCOVA Model[a]) in Trial 0013

	Xeomin®		Botox®		Difference Xeomin® - Botox®
PP Analysis	n	N=213	n	N=207	
Mean score at baseline (SD)	213	17.8 (3.5)	207	17.7 (3.7)	

Mean score at control visit (SD)	213	11.1 (4.8)	207	11.4 (4.8)	
Mean change [95%CI]	213	-7.0 [-7.6, -6.3][b]	207	-6.6 [-7.3, -6.0][b]	-0.33 (-1.05, 0.38)[a]
mITT Analysis	n	N=231	n	N=232	
Mean score at baseline (SD)	230	17.7 (3.5)	232	17.8 (3.7)[b]	
Mean score at control visit (SD)	230	11.2 (4.8)	228	11.5 (4.9)	
Mean change [95%CI]	230	-6.8 [-7.4, -6.3][b]	228	-6.5 [-7.1, -6.0][b]	-0.29 (-0.98, 0.40)[a]

mITT = modified intention-to-treat; PP = per protocol; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale

[a] The final ANCOVA model only included those independent variables that, in a backward selection procedure, presented a p≤0.2.

[b] Least squares mean change

Note: Mean (SD) time to control visit was 28.4 (2.6) days for Xeomin and 28.2 (2.4) days for Botox

6.7 The submission claimed that as the upper bound of the 95% confidence interval (CI) did not exceed the pre-specified non-inferiority margin of 1.3 points, Xeomin® can be considered non-inferior to Botox® in the treatment of cervical dystonia. The upper bound of the 95%CI was 0.38 points in the per protocol (PP) analysis and 0.40 points for the intention-to-treat (ITT) analysis; differences of this magnitude were unlikely to be clinically important.

6.8 Response, as measured by the TWSTRS - Severity score, was only assessed at the control visit (28 ± 7 days) and at the final visit (when the TWSTRS Severity score had reached at least 80% of the baseline value or at the latest 112 days after injection, median 110 days). It is possible that the pharmacokinetics of the two preparations differ; therefore, analysis at these two time points did not provide a reliable measure of the relative treatment effect over the entire duration of likely effectiveness.

6.9 The ESC noted that Trial 0013 presented TWSTRS Severity score, TWSTRS Pain Subscore, the Visual Analogus Scale (VAS) Pain score and the Patient Evaluation of Global Response (PEGR). There were no statistically significant differences between the two treatment groups for any of these outcomes at both control and final visits. The ESC considered that Xeomin® is non-inferior in efficacy in the treatment of cervical dystonia compared to Botox® at a 1:1 dose ratio.

Blepharospasm

6.10 The results of the primary outcome in Trial 0003, the change from baseline in scores on the Jankovic Rating Scale at the control visit (Day 21±1), are presented in the table below.

Change from baseline to control visit (Day 21±1) in Jankovic Rating Scale sum score[a] (final ANCOVA model[b]) in Trial 0003

	Xeomin®		Botox®		Difference Xeomin®– Botox®
PP Analysis	n	N=129	n	N=127	
Mean score at baseline (SD)	129	5.3 (1.5)	127	5.4 (1.5)	
Mean score at control visit (SD)	129	2.5 (2.0)	127	2.8 (2.1)	
LS mean change (SE) [95% CI]	129	-2.9 (0.2) [-3.2, -2.6]	127	-2.7 (0.2) [-3.0, -2.4]	-0.23 [-0.68, 0.22]
mITT Analysis	n	N=148	n	N=152	
Mean score at baseline (SD)	148	5.2 (1.6)	152	5.5 (1.5)	
Mean score at control visit (SD)	144	2.4 (2.0)	149	2.9 (2.1)	

LS mean change (SE) [95% CI]	144	-3.0 (0.2) [-3.3, -2.7]	149	-2.7 (0.2) [-3.0, -2.4]	-0.31 [-0.73, 0.12]

ANCOVA = analysis of covariance; SD = standard deviation; LS = least squares; SE = standard error; CI = confidence interval; PP = per protocol; mITT = modified intention-to-treat

[a] Scores on the Jankovic Rating Scale range from 0 to 8. A decrease in the Jankovic Rating Scale score indicates an improvement of severity and/or frequency of blepharospasm symptoms

[b] Final ANCOVA model included those variables having an influence on the primary efficacy variable of p<0.2. These covariates were: baseline mean Jankovic Rating Scale score (F value =27.66, p<0.001), pooled country (F value =3.62, p=0.007) and dose (F value =6.81, p=0.01). For comparison, full ANCOVA model results for the PP population were (difference: -0.3; 95%CI: [-0.7, 0.2], p=0.292).

6.11 The difference in the least square mean changes in the Jankovic Rating Scale scores between the two treatment groups numerically favoured Xeomin® at Week 4. In both the PP analysis and the ITT analysis, the whole CIs of the differences were within the minimum clinically important difference (MCID) pre-specified in the trial protocol, suggesting non-inferior treatment efficacy.

6.12 Results of the secondary outcome of the change from baseline in Blepharospasm Disability Index scores were consistent with the results of the primary endpoint.

6.13 The ESC considered that Xeomin® is non-inferior in efficacy in the treatment of blepharospasm compared to Botox® at a 1:1 dose ratio.

Upper limb spasticity following a stroke

6.14 Indirect comparisons were performed comparing the Week 4, Week 12 and final visit (Week 12-20) data in Trial 0410 with the Botox® results presented in the July 2008 Botox® Public Summary Document (PSD), respectively, as the PSD did not provide the follow-up time period at which the mean changes from baseline in Ashworth scores were assessed in the Botox® trials. Results are presented in the table below.

Indirect comparison: change in Ashworth scores[a] from baseline

Trial ID	Trial of Xeomin®			Trials of Botox®			Indirect comparison Absolute difference[c] [95% CI]
	Difference[b] [95% CI]	Xeomin® N Mean (SD)	Placebo N Mean (SD)	Placebo N Mean (SD)[c]	Botox® N Mean (SD)	Difference [95% CI]	
Elbow flexor							
Trial 0410 Week 4	-0.36 [-0.59, -0.13]	N=54 -0.72 (0.63)	N=55 -0.36 (0.59)	–	–	–	[redacted]
Trial 0410 Week12	-0.26 [-0.48, -0.03]	N=54 -0.52 (0.67)	N=54 -0.26 (0.52)	–	–	–	[redacted]
Trial 0410 Final visit	-0.20 [-0.42, 0.01]	N=54 -0.41 (0.60)	N=54 -0.20 (0.53)	–	–	–	[redacted]
BOTOX® Pooled[d]	–	–	–	-0.30 [-0.52, -0.1]			[redacted]
Wrist flexor							
Trial 0410 Week 4	-0.49 [-0.72, -0.26]	N=73 -0.88 (0.76)	N=72 -0.39 (0.64)	–	–	–	[redacted]
Trial 0410 Week 12	-0.37 [-0.6, -0.13]	N=71 -0.56 (0.81)	N=71 -0.20 (0.62)	–	–	–	[redacted]
Trial 0410 Final visit	-0.20 [-0.42, 0.01]	N=54 -0.41 (0.60)	N=54 -0.20 (0.53)	–	–	–	[redacted]
BOTOX® Pooled[d]	–	–	–	-0.74 [-1.05, -0.42]			[redacted]
Finger flexor							
Trial 0410	-0.62	N=73	N=74	–	–	–	[redacted]

Week 4	[-0.88, -0.36]	-1.01 (0.92)	-0.39 (0.68)				[redacted]
Trial 0410 Week 12	-0.36 [-0.61, -0.11]	N=71 -0.63 (0.87)	N=73 -0.27 (0.63)	–	–	–	
Trial 0410 Final visit	-0.17 [-0.37, 0.03]	N=72 -0.35 (0.65)	N=73 -0.18 (0.56)	–	–	–	
BOTOX® Pooled[d]	–	–	–	-0.26 [-0.75, 0.22]			

SD = standard deviation; CI = confidence interval

Bold indicates indirect comparison

[a] Scores on the Ashworth Scale range from 0 to 4. A decrease in the Ashworth score indicates an improvement of spasticity.

[b] Xeomin® *vs* placebo.

[c] Xeomin® *vs* Botox®

[d] Weighted mean difference. Botox® vs placebo. The mean changes in the (Expanded) Ashworth score in each of the treatment arms and the results of the test for heterogeneity were not reported in the July 2008 PBAC Public Summary Document

6.15 Compared with relevant Botox® results, the point estimates of the indirect comparisons favoured Xeomin® in finger flexors and elbow flexors when using the Week 4 results in the Xeomin® trial. However, this direction would be inverted when comparing the final data from the Xeomin® trial with the Botox® results published in the PSD. The indirect results numerically favoured Botox® for wrist flexors no matter what time point in the Xeomin® trial were used (Week 4, Week 12 or the final visit). No firm non-inferiority conclusion can be drawn from the indirect comparison, given the following concerns: 1) the violation of the underpinning exchangeability assumptions; 2) the validity of the Ashworth Scale as a measure of spasticity in the proposed population; and 3) the lack of well-justified MCID in the continuous variable of the change in Ashworth scores.

6.16 While the PBAC recommended the listing of Botox® for treatment of post-stroke spasticity of the upper limb, using Dysport® as the comparator, the response rate ($\geqslant$ 2 points reduction in Ashworth scores in <u>any muscle/joint</u>) was considered, in addition to the change in Ashworth scores, as a clinically relevant outcome. However, as the Xeomin® trial used a different definition for treatment response ($\geqslant$2 point reduction in Ashworth scores in <u>wrist flexors</u>), a meaningful indirect comparison of the response rates reported in the Xeomin® and Botox® trials was not possible.

6.17 The ESC agreed that results from the indirect comparison may not be reliable due to exchangeability issues. However, the ESC considered that Xeomin® and Botox® are likely to have similar clinical effects on the treatment of post-stroke upper limb spasticity as they are analogues of each other and the two head to head trials have shown non-inferior efficacy between these two products in the treatment of cervical dystonia and blepharospasm.

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

Comparative harms

<u>Cervical dystonia</u>

6.18 A summary of the adverse event (AE) in Trial 0013, for cervical dystonia, is presented in the table below.

Summary of key adverse events in the direct randomised trial 0013[a]

	Xeomin® N = 231	Botox® N= 232	Risk difference[b] [95% CI]	Relative risk[b] [95% CI]
Any adverse events	65 (28.1%)	56 (24.1%)	4.0% [-4.0%, 12.0%]	1.17 [0.86, 1.59]
Adverse events	15 (6.5%)	9 (3.9%)	2.6% [-1.4%, 6.6%]	1.67 [0.75, 3.75]

considered study treatment-related				
Severe adverse event	3 (1.3%)	3 (1.3%)	0.0% [-2.1%, 2.1%]	1.00 (0.20, 4.92)
Serious adverse event	4 (1.7%)	5 (2.2%)	-0.4% [-2.9%, 2.1%]	0.80 [0.22, 2.95]
Adverse event leading to withdrawal	0 (0.0%)	1 (0.4%)	–	–
Death	0 (0.0%)	0 (0.0%)	–	–

[a] Only patients who had a previous stable response to Botox were included in the trial
[b] Risk differences and relative risks were calculated during the evaluation

6.19 The AEs most frequently reported mainly involved the gastrointestinal system (Xeomin® 13.4%, Botox® 11.2%, predominantly dysphagia) and the musculoskeletal system (Xeomin® 8.2%, Botox® 4.7%, mainly skeletal and back pain). A higher proportion of patients experienced treatment-related AEs in the Xeomin® group, compared to the Botox® group. In addition, both dysphagia and musculoskeletal disorders were more frequent following Xeomin® than following Botox®. As patients were required to have documented stable response to Botox® patients who experienced an AE to Botox® therapy were unlikely to have been included in the trial. It was possible that the rate of AEs, for both treatments, may be higher in clinical practice, where the population will include treatment-naïve patients.

Blepharospasm

6.20 A summary of key adverse events in Trial 0003 is presented in the table below.

Summary of key adverse events in Trial 0003

	Xeomin® N = 148	Botox® N= 155	Risk difference[a] [95% CI]	Relative risk[a] [95% CI]
Any adverse events	40 (27.0%)	45 (29.0%)	-2.0% [-12.1, 8.1%]	0.93 [0.65, 1.34]
Adverse events considered study treatment-related	18 (12.2%)	13 (8.4%)	3.8% [-3.1%, 10.6%]	1.45 [0.74, 2.85]
Serious adverse event	3 (2.0%)	5 (3.2%)	-1.2% [-4.8%, 2.4%]	0.63 [0.15, 2.58]
Severe adverse event	3 (2.0%)	1 (0.6%)	1.4% [-1.2%, 4.0%]	3.14 [0.33, 29.87]
Adverse event leading to withdrawal	0 (0.0%)	0 (0.0%)	–	–
Death	0 (0.0%)	0 (0.0%)	–	–

CI = confidence interval
[a] Risk differences and relative risks were calculated during the evaluation

6.21 AEs occurred in 40 patients (27.0%) in the Xeomin® group and in 45 patients (29.0%) in the Botox® group. The most common AE was ptosis, which was reported by 6.1% of patients in the Xeomin® group and by 4.5% patients in the Botox® group. The other AEs reported more frequently in patients treated with Xeomin® were gastrointestinal system disorders (6 patients (4.1%) *vs* 1 patient (0.6%) in the Botox® group). Higher proportions of patients receiving Xeomin® developed drug-related AEs (12.2% vs 8.4%) and severe AEs (2.0% vs 0.6%). The trial, however, was not sufficiently powered to detect a statistically significant difference between the two treatments. Of the severe AEs reported, only the ptosis AE (in the Xeomin® arm) was considered to be associated with therapy.

Upper limb spasticity following a stroke

6.22 The submission did not present any evidence indicating the comparative safety of Xeomin® over Botox® in this population.

Comparative benefits and harms

6.23 A summary of comparative benefits and harms for Xeomin®, versus Botox® in cervical dystonia patients is presented in the table below.

Summary of comparative benefits and harms for Xeomin® and Botox® in cervical dystonia patients

Benefits							
	Xeomin®			Botox®			Difference: Xeomin® vs. Botox® [95% CI]
	n	LS mean change	SE	n	LS mean change	SE	
Change from baseline to Day 28±7 in TWSTRS -Severity scores[a]							MCID: 1.3
Trial 0013	213	-7.0	0.3	207	-6.6	0.3	-0.33 [-1.05, 0.38]

Harms						
Trial	Xeomin®	Botox®	RR [95% CI]	Event rate/100 patients		RD [95% CI]
				Xeomin®	Botox®	
Any adverse events						
Trial 0013	65/231	56/232	1.17 [0.86, 1.59]	28.1	24.1	4.0% [-4.0%, 12.0%]
Any drug-related adverse events						
Trial 0013	15/231	9/232	1.67 [0.75, 3.75]	6.5	3.9	2.6% [-1.4%, 6.6%]
Any severe adverse events						
Trial 0013	3/231	3/232	1.00 [0.20, 4.92]	1.3	1.3	0.0% [-2.1%, 2.1%]

[a] Scores on the TWSTRS- Severity scale range from 0-35. A decrease in score indicates an improvement in dystonic movement symptoms. Results of the per protocol analysis using the final ANCOVA model are presented.
Source: Compiled during the evaluation

6.24 On the basis of the head to head trial, Xeomin® appears to have the same effect as Botox® in the treatment of cervical dystonia.

6.25 On the basis of the head to head trial presented, the frequency of adverse effects appears to be the same.

6.26 A summary of comparative benefits and harms for Xeomin® and Botox® in blepharospasm patients is presented in the table below.

Summary of comparative benefits and harms for Xeomin® and Botox® in blepharospasm patients

Benefits							
	Xeomin®			Botox®			Difference: Xeomin® vs. Botox® [95% CI]
	n	LS mean change	SE	n	LS mean change	SE	
Change from baseline to Day 21±1 in Jankovic Rating Scale sum scores[a] (MCID: 0.8)							
Trial 0003	129	-2.9	0.2	127	-2.7	0.2	-0.23 [-0.68, 0.22]
Change from baseline to Day 21±1 in Jankovic Rating Scale sum scores[b] (MCID: not specified)							
Trial 0003	129	-0.8	0.1	125	-0.8	0.1	-0.01 [-0.16, 0.14]

Harms[c]						
	Xeomin® n/N	Botox® n/N	RR [95% CI]	Event rate/100 patients		RD [95% CI]
				Xeomin®	Botox®	
Any adverse events						
Trial 0003	40/148	45/155	0.93 [0.65, 1.34]	27.0	29.0	-2.0% [-12.1, 8.1%]
Any drug-related adverse events						
Trial 0003	18/148	13/155	1.45 [0.74, 2.85]	12.2	8.4	3.8% [-3.1%, 10.6%]
Any severe adverse events						

Trial 0003	3/148	1/155	3.14 [0.33, 29.87]	2.0	0.6	1.4% [-1.2%, 4.0%]

LS = least square; SE = standard error; CI = confidence interval; MCID = minimal clinically important difference specified as the non-inferiority margin in the submission; RR = relative risk; RD = risk difference

[a] Scores on the Jankovic Rating Scale range from 0 to 8. A decrease in the Jankovic Rating Scale score indicates an improvement of severity and/or frequency of blepharospasm symptoms. Results of the per protocol analysis using the final ANCOVA model are presented.

[b] Scores on the Blepharospasm Disability Index range from 0 to 4. A decrease in the Blepharospasm Disability Index score indicates an improvement of functional impairment. Results of the per protocol analysis using the final ANCOVA model are presented.

[c] Adverse events were reported until 4 weeks after a patient underwent a final examination as part of the trial.

Source: Compiled during the evaluation

6.27 On the basis of the head to head trial, Xeomin® appears to have the same effect as Botox® in the treatment of blepharospasm.

6.28 On the basis of the head to head trial presented, the frequency of adverse effects appears to the same.

6.29 A summary of comparative benefits for Xeomin® and Botox® in patients with post-stroke upper limb spasticity is presented in the table below.

Summary of comparative benefits for Xeomin® and Botox® in patients with post-stroke upper limb spasticity[a]

Trial ID	Trial of Xeomin®			Trials of Botox®			Indirect comparison absolute difference [95% CI]
	Difference [95% CI]	Xeomin® N Mean (SD)	Placebo N Mean (SD)	Placebo N Mean (SD)[c]	Botox® N Mean (SD)	Difference [95% CI]	
Benefits							
Change from baseline in scores on the Ashworth scale[b] for elbow flexors (MCID: not specified)							
Trial 0410 Week 4	-0.36 [-0.59, -0.13]	N=54 -0.72 (0.63)	N=55 -0.36 (0.59)	–	–	–	
Botox® Pooled[c]	–	–	–	-0.30 [-0.52, -0.1]			
Change from baseline in scores on the Ashworth scale[b] for wrist flexors (MCID: not specified)							
Trial 0410 Week 4	-0.49 [-0.72, -0.26]	N=73 -0.88 (0.76)	N=72 -0.39 (0.64)	–	–	–	
Botox® Pooled[c]	–	–	–	-0.74 [-1.05, -0.42]			
Change from baseline in scores on the Ashworth scale[b] for finger flexors (MCID: not specified)							
Trial 0410 Week 4	-0.62 [-0.88, -0.36]	N=73 -1.01 (0.92)	N=74 -0.39 (0.68)	–	–	–	
Botox® Pooled[c]	–	–	–	-0.26 [-0.75, 0.22]			
Harms							
No comparative evidence provided.							

SD = standard deviation; CI = confidence interval; MCID = minimal clinically important difference specified as the non-inferiority margin in the submission

Bold indicates indirect comparison

[a] The submission does provide any evidence regarding the comparative safety of Xeomin® *versus* Botox® in this population.

[b] Scores on the Ashworth Scale range from 0 to 4. A decrease in the Ashworth score indicates an improvement of spasticity.

[c] Weighted mean difference

Source: Compiled during the evaluation

6.30 On the basis of the indirect comparisons, Xeomin® appears to be no worse than Botox® in the treatment of post-stroke upper limb spasticity.

6.31 While evidence comparing the safety of Xeomin® versus Botox® for treatment of post-stroke upper limb spasticity was not provided in the submission, the ESC considered that Xeomin® and Botox® are likely to have similar safety profile in the treatment of post-stroke upper limb spasticity as they are analogues of each other and direct evidence presented for the cervical dystonia and blepharospasm indications also showed non-inferiority in comparative safety at a 1:1 dose ratio.

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

Clinical claim

6.32 The submission described Xeomin® as non-inferior in terms of comparative effectiveness and safety for treatment of cervical dystonia, blepharospasm and post-stroke upper limb spasticity compared with Botox®.

6.33 The ESC considered the clinical claims are reasonable.

Economic analysis

6.34 The submission presented a cost-minimisation analysis. The equi-effective doses were estimated as:

- Cervical dystonia: 140.4U of Xeomin® over approximately 110 days and Botox® 140.4U over approximately 110 days;
- Blepharospasm: 40.7U of Xeomin® over approximately 110 days and Botox® 40.7U over approximately 110 days; and
- Post-stroke spasticity of the upper limb: 229U of Xeomin® over approximately 87 days and 229U Botox® over approximately 87 days.

6.35 Dosing relativity and duration of treatment effect were taken from the direct trials of Xeomin® vs Botox® (0013 and 0003). In the absence of a head to head trial of Xeomin® vs Botox® in patients with post-stroke spasticity of the upper limb, the submission has assumed the same dosing relativity as those with cervical dystonia and blepharospasm (eg 1 U Xeomin® : 1 U Botox®).

6.36 Xeomin® does not require additional resources beyond those used to treat patients with Botox®, therefore a cost minimisation approach based solely on the cost of Botox® and Xeomin® is appropriate.

6.37 The cost minimisation analysis presented by the submission is appropriate if PBAC accepts the submission's claim of non-inferiority.

Drug cost/patient/administration

6.38 Based on average doses of 40.7U, 140.4U and 229U in the trials of blepharospasm, cervical dystonia and post-stroke upper limb spasticity, respectively, drug cost per patient per administration is $415.50 for blepharospasm, $831.00 for cervical dystonia and $1,246.50 for post-stroke upper limb spasticity.

Estimated PBS usage & financial implications

6.39 This submission was not considered by DUSC as Xeomin® is assumed to substitute for Botox® and Dysport® and the proposed price of Xeomin® is the same as that of Botox®.

[redacted]

6.40 The submission claimed no growth in the overall market for botulinum toxins due to PBS listing of Xeomin®, and anticipated Xeomin® use to be completely offset by the use of Botox® and Dysport®. The reduction in each treatment is expected to be proportional to current market shares of Botox® [redacted] and Dysport®. The submission assumed Xeomin® will take [redacted] of the market share relative to Botox® and Dysport® in the first year of the PBS listing reaching [redacted] by the fifth year. Although uncertain, projected market uptake rates of Xeomin® will not have impact on net financial implications to the PBS/MBS.

6.41 The submission assumed that there will be no financial impact of this listing to the MBS as every MBS item processed for the administration of Xeomin® will be offset by a corresponding decrease in the number of items processed for Botox® or Dysport®. The cost savings shown in the table above are likely due to the slight misalignment between the cost-minimising price of Xeomin® relative to the two formulations of Dysport®.

6.42 The requested listing of Xeomin® is based on the equivalent efficacy and safety to the main comparators, Botox® and Dysport®, therefore is not expected to have any financial implications for any government health budgets outside the PBS and MBS.

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

7 PBAC Outcome

7.1 The PBAC recommended the listing of incobotulinum toxin A (Xeomin®) 100LD50 units injection, on a cost-minimisation basis compared with Botox®. The PBAC agreed that it should be available only under special arrangements under Section 100 – Botulinum Toxin Program and coordinated with corresponding amendments to the MBS item descriptors, as required. The PBAC also recommended that this listing should be coordinated with corresponding listings of related MBS items to administer incobotulinum toxin A for the three recommended indications, which is the subject of a coordinated submission to MSAC.

7.2 The PBAC agreed that the prescribing of Xeomin® for cervical dystonia, blepharospasm and post-stroke spasticity of the upper limb should be restricted to medical practitioners who hold specialist qualifications and are registered to prescribe botulinum toxin.

7.3 The PBAC accepted the cost-minimisation analysis for the three indications with equi-effective doses estimated as: cervical dystonia: 140.4U of Xeomin® over approximately 110 days and Botox® 140.4U over approximately 110 days; blepharospasm: 40.7U of Xeomin® over approximately 110 days and Botox® 40.7U over approximately 110 days; and post-stroke spasticity of the upper limb: 229U of Xeomin® over approximately 87 days and 229U Botox® over approximately 87 days.

7.4 The PBAC agreed with the ESC that the eligibility criterion in the requested Xeomin® restriction for treatment of upper limb spasticity should be revised to read "Maximum number of treatments to be authorised is 4 (total Xeomin®, Botox® and Dysport®) per upper limb per lifetime". The PBAC considered that a similar change should flow-on to the current listings for Botox® and Dysport® and requested the Department to amend current restrictions for Botox® and Dysport® for this indication.

7.5 The PBAC accepted the proposed clinical place for Xeomin®, as an alternative form of botulinum toxin A for the treatment of cervical dystonia, blepharospasm and post-stroke spasticity of the upper limb.

7.6 The PBAC accepted Botox® as the appropriate comparator.

7.7 The PBAC agreed that Xeomin® is non-inferior in efficacy in the treatment of cervical dystonia and blepharospasm compared to Botox® at a 1:1 dose ratio. The PBAC agreed with the ESC that although the indirect comparison of Xeomin® with Botox® for the post-stroke upper limb spasticity indication is less reliable due to exchangeability issues, the conclusion of non-inferiority was supported by the evidence presented from the head-to-head trials for the other two indications (cervical dystonia and blepharospasm), which showed non-inferiority in comparative efficacy at a 1:1 dose ratio.

7.8 The PBAC agreed that Xeomin® is non-inferior in terms of harms in the treatment of cervical dystonia and blepharospasm compared to Botox® at a 1:1 dose ratio. The

PBAC agreed with the ESC that whilst the submission did not present any evidence indicating the comparative safety of Xeomin® over Botox® in the post-stroke upper limb spasticity indication, the evidence presented for the cervical dystonia and blepharospasm indications also showed non-inferiority in comparative safety at a 1:1 dose ratio.

7.9 The PBAC noted the estimated PBS usage and financial implications presented in the submission which assumed no financial impact to PBS and MBS because of cost offset by a corresponding decrease in the number of items processed for Botox® and Dysport®. The PBAC considered this was reasonable.

7.10 The PBAC recommended that Xeomin® should be treated as interchangeable on an individual patient basis with Botox® and Dysport®.

7.11 The PBAC advised that Xeomin® is not suitable for prescribing by nurse practitioners.

7.12 The PBAC recommended that the Safety Net 20 Day Rule should not apply.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty (packs)	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
INCOBOTULINUM TOXIN A Injection, 100 units vial	1	$415.50	Xeomin Merz

Program:	Section 100 Botulinum Toxin program
Episodicity:	
Severity:	
Condition:	Spasmodic torticollis
Indication:	Spasmodic torticollis
Criteria for availability:	Restricted benefit
Clinical criteria:	The treatment must be as monotherapy; or The treatment must be as adjunctive therapy to current standard care.
Administrative advice:	NOTE Arrangements to prescribe this item should be made by medical practitioners with the Department of Human Services, contact telephone number 1800 700 270. NOTE The units used to express the potency of botulinum toxin preparations currently available for PBS subsidy are not equivalent.

Program:	Section 100 Botulinum Toxin program

Episodicity:	
Severity:	
Condition:	Blepharospasm or hemifacial spasm
Indication:	Blepharospasm or hemifacial spasm
Criteria for availability:	Restricted benefit
Clinical criteria:	Treatment of blepharospasm in adults
Population criteria:	Patient must be an adult.
Administrative advice:	NOTE Arrangements to prescribe this item should be made by medical practitioners with the Department of Human Services, contact telephone number 1800 700 270. NOTE The units used to express the potency of botulinum toxin preparations currently available for PBS subsidy are not equivalent.

Program:	Section 100 Botulinum Toxin program
Episodicity:	
Severity:	Moderate to severe
Condition:	spasticity of the upper limb following a stroke
Indication:	Moderate to severe spasticity of the upper limb following stroke
Criteria for availability:	Restricted benefit
Clinical criteria:	The treatment must be used as second line therapy when standard management has failed (e.g. physiotherapy and/or oral spasticity agents) or as an adjunct to physical therapy.
Population criteria:	Patient must be an adult.
Prescriber Instructions:	Moderate to severe spasticity is defined as MAS greater than or equal to 3 using Modified Ashworth Scale. Maximum number of treatments to be authorised is 4 *(total Xeomin®, Botox® and Dysport®)* per upper limb per lifetime. Treatment should not be initiated until 3 months post-stroke in patients who do not have established severe contracture. Treatment should be discontinued if the patient does not respond (decrease of MAS greater than 1 in at least one joint) after two treatments. The date of the stroke must be provided. Contraindications to treatment include established severe contracture and known sensitivity to botulinum neurotoxin.
Administrative advice:	Note Arrangement to prescribe this item should be made by medical practitioners with the Department of Human Services, contact telephone number 1800 700 270. Note The units used to express the potency of botulinum toxin preparations currently available for PBS subsidy are not equivalent.

9 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.

10 Sponsor's Comment

The sponsor agrees with the PBAC's assessment of Xeomin and thanks the PBAC for the positive recommendation to list Xeomin as a treatment option for blepharospasm, cervical dystonia and post-stroke spasticity of the upper limb on the PBS.