Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1808 – IncobotulinumtoxinA (XEOMIN) injection for lower- and upper-limb spasticity associated with cerebral palsy in patients 2 years and older

Applicant: **Merz Australia**

Date of MSAC consideration: **31 July 2025**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

This codependent application requested:

- Amendment of existing Medicare Benefits Schedule (MBS) items 18354 and 18361 to include injection of incobotulinumtoxinA (Xeomin®) along with Botulinum Toxin Type A Purified Neurotoxin Complex (Botox®) or Clostridium Botulinum Type A Toxin-Haemagglutinin Complex (Dysport®); and
- Pharmaceutical Benefits Scheme (PBS) Authority Required listing of incobotulinumtoxinA (Xeomin®) for treatment of spasticity of the upper and/or lower limbs associated with cerebral palsy (CP) in patients 2 years and older.
- This streamlined ADAR was eligible for direct consideration by MSAC and therefore bypassed PASC and ESC.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC supported the amendment of existing MBS items 18354 and 18361 to include the injection of Xeomin® for the treatment of upper and lower limb spasticity in patients with cerebral palsy (CP) aged 2 years and older. MSAC noted at its July 2025 meeting, the Pharmaceutical Benefits Advisory Committee (PBAC) recommended PBS listing of Xeomin® for the treatment of moderate to severe spasticity of the upper limb and dynamic equinus foot deformity due to spasticity, in patients with CP aged 2 years and older. MSAC noted PBAC was satisfied that Xeomin® was non-inferior to the nominated comparator Botox® in terms of efficacy and safety. The existing MBS items already allow the botulinum toxin products Botox® and Dysport® to be used for this purpose.

MSAC noted the amendment would not result in a change in associated management as there would be no change to either MBS item with regard to the practitioners, item fee, item category or use of anaesthesia and ultrasound where required.

MSAC supported the following MBS item descriptor amendments (in red and bold):

Category 3 – THERAPEUTIC PROCEDURES
MBS item **18354** Botulinum Toxin Type A Purified Neurot**o**xin Complex (Botox), Clostridium Botulinum Type A Toxin-Haemagglutinin Complex (Dysport), **or incobotulinumtoxinA (Xeomin)**, injection of, for the treatment of dynamic equinus foot deformity (including equinovarus and equinovalgus) due to spasticity **from** cerebral palsy, if: (a) the patient is at least 2 years of age; and (b) the treatment is for all or any of the muscles subserving one functional activity and supplied by one motor nerve, with a maximum of 4 sets of injections for the patient on any one day (with a maximum of 2 sets of injections for each lower limb), including all injections per set (Anaes.)
Fee: $145.65 Benefit: 75% = $109.25 85% = $123.85

Category 3 – THERAPEUTIC PROCEDURES
MBS item 18361 Clostridium Botulinum Type A Toxin-Haemagglutinin Complex (Dysport), Botulinum Toxin Type A Purified Neurotoxin Complex (Botox), or **incobotulinumtoxinA (Xeomin)**, injection of, for the treatment of moderate to severe upper limb spasticity due to cerebral palsy if: (a) the patient is at least 2 years of age; and (b) the treatment is for all or any of the muscles subserving one functional activity and supplied by one motor nerve, with a maximum of 4 sets of injections for the patient on any one day (with a maximum of 2 sets of injections for each upper limb), including all injections per set (Anaes.)
Fee: $145.65 Benefit: 75% = $109.25 85% = $123.85

Consumer summary

This co-dependent application from Merz Australia Pty Ltd that requested amendment of MBS items 18354 and 18361 to include incobotulinumtoxinA (Xeomin®) injections for patients aged 2 years and older with cerebral palsy (CP) who have moderate to severe spasticity (stiffness) of their upper or lower limb. The PBAC recommended listing of Xeomin® on the PBS at its July 2025 meeting, having considered the drug to be safe and effective.

CP is a group of nervous system (neurological) disorders that first appear in babies or young children. CP affects a person's ability to control body movement and coordination. Spasticity, or stiffness, affects approximately 70–90% of children with CP. Spasticity can affect the upper limbs (arms) or lower limbs (legs) and can cause problems with pain and movement.

Xeomin® is a medication that is a form of botulinum toxin, that is similar to medications such as Botox® and Dysport®, that are also botulinum toxin products. Botox® and Dysport® all work to reduce spasticity (stiffness). When Xeomin® is injected into muscles that are affected by spasticity, it helps the muscles to relax by blocking the chemical signals that cause muscles to stiffen. MBS items 18354 and 18361 already exist for the injection of Botox® and Dysport® to treat spasticity in patients aged 2 years and older with upper and/or lower limb spasticity. This application proposes to add Xeomin® to these MBS items, to provide another choice of medication that can used.

Consumer summary
MSAC noted that this application included evidence for Xeomin® use in children only. MSAC agreed with PBAC and considered it appropriate for the treatment to also be available for adults as well, as there are no safety or effectiveness issues in the adult population. MSAC noted this application limited Xeomin® injections to once every 12 weeks. MSAC noted that Botox® and Dysport® do not have frequency restrictions and thus considered that frequency restrictions for Xeomin® injections are not required. MSAC noted that MBS items 18354 and 18361 already exist for the injection of the drugs Botox® and Dysport® for spasticity in CP. MSAC considered that including Xeomin® in these existing MBS items would not change the overall cost of the service which would remain the same, as Xeomin® is expected to be used instead of, not in addition to, Botox® or Dysport® by allowing doctors and patients to have a choice of 3 medications to use. For this same reason, MSAC considered it would also not increase the overall use of this service and associated services (which includes anaesthesia and ultrasounds when needed). **MSAC's advice to the Commonwealth Minister for Health, Disability and Ageing** MSAC supported amending MBS items 18354 and 18361 to include Xeomin®. The PBAC considered the drug to be safe and effective. MSAC considered that there would be no to minimal financial impact and no change to resources if Xeomin® were included in MBS items 18354 and 18361.

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

MSAC noted that this is a co-dependent application from Merz Australia Pty Ltd for the amendment of Medicare Benefits Schedule (MBS) items 18354 and 18361 to include incobotulinumtoxinA (Xeomin®) alongside botulinum toxin type A purified neurotoxin complex (Botox®) and clostridium botulinum type A toxin-haemagglutinin complex (Dysport®) to treat spasticity of the upper and/or lower limbs associated with CP in patients aged 2 years and older.

CP is a group of neurological disorders that appear in infancy or early childhood and permanently affect body movement and muscle coordination. Spasticity affects approximately 70–90% of children with the disorder.

MSAC noted that at its July 2025 meeting, the Pharmaceutical Benefits Advisory Committee (PBAC) recommended listing of Xeomin® on the Pharmaceutical Benefits Scheme (PBS) for the treatment of moderate to severe spasticity of the upper limb and dynamic equinus foot deformity due to spasticity in patients with CP aged 2 years and older. The PBAC was satisfied that Xeomin® was non-inferior to the nominated comparator Botox® in terms of efficacy and safety. The PBAC considered that although the Xeomin® trials were conducted in the paediatric population, provided that fixed contractures had not developed, there would be no clinical reason to expect a lack of effectiveness in adults. Given the nature of the therapy, treatment was unlikely to be continued if no effect was observed. The PBAC considered Dysport® was also a relevant comparator and recommended listing on a cost-minimisation basis. The PBAC considered the equi-effective doses of 1 U Xeomin® = 1 U Botox® and 1 U Xeomin® = 2.5 U Dysport®.

MSAC noted and welcomed the public consultation input, which was supportive of listing Xeomin®. The Rehabilitation Medicine Society of Australia and New Zealand (RMSANZ) noted the various clinical specialty areas that currently provide this service. Cerebral Palsy Alliance (CPA)

queried including 'ambulant' in the MBS descriptor, which MSAC noted was in the requested PBS restriction and advised that it should be considered by the department during implementation.

MSAC noted the population was patients with CP aged 2 years and older with both or either:

- moderate to severe spasticity of the upper limb
- dynamic equinus foot deformity due to spasticity.

MSAC noted that Xeomin® was compared to Botox® and Dysport® with Botox® the nominated comparator as it is the market-leading injectable toxin for the indications sought and has a 1:1 dose equivalence with Xeomin®. The pattern of substitution would be partial, with Botox® substituted at the uptake rate for Xeomin® of redacted% in year 1, redacted% in year 2 and redacted% in years 3 and 4. MSAC noted that the vast majority of the substitution would be of Botox®, but a small fraction of Dysport® may also be substituted.

MSAC noted that the outcomes were improvement in muscle tone and motor function for children with CP spasticity in lower and/or upper limb(s); and adverse events (AEs).

MSAC noted the clinical evidence was considered by PBAC, which comprised the TIM/TIMO phase 3 studies. These studies revealed a favourable safety and tolerability profile, with high retention rates.

MSAC noted that, in a comparative safety study, Xeomin® and Botox® safety were comparable. All AEs were mild to moderate, and all events resolved. No study discontinuations in either treatment group were due to AEs.

MSAC noted that the phase 3 clinical trials demonstrated that treatment with Xeomin® offers significant and consistent improvement in muscle tone and motor function for children with CP spasticity in lower and/or upper limb(s).

Although the trials on which the evidence was based used a paediatric population, MSAC agreed with the PBAC and considered it appropriate for this service to be available to both paediatric and adult patients. MSAC considered it unlikely that this treatment would be used inappropriately in adults, and there would be no additional safety issues for adults.

MSAC noted the economic evaluation used a cost-minimisation approach, with Botox® as the main comparator. MSAC considered that Xeomin® would provide an alternate option to the currently listed botulinum toxin treatments and as such would not increase the MBS utilisation of items 18354 and 18361 as these items would still be claimed regardless of the prescribed PBS treatment.

MSAC noted the existing MBS items were for injections of Botox® or Dysport® in the lower limb (MBS item 18354) and upper limb (MBS item 18361) and that the only amendment would be to the item descriptor to include Xeomin® which would not change the associated fees ($145.65). MSAC also noted that the MBS item descriptor 18354 that should be corrected to refer to a 'neurotoxin'.

MSAC noted that listing Xeomin® on the PBS would not change the current clinical management algorithm as there would be no change to resources or practitioners providing the service if Xeomin® is substituted, including no change in use of anaesthesia or ultrasound where required. The service would remain a Type C procedure. As noted by the RMSANZ, various specialists provide this service, including neurologists, rehabilitation specialists, paediatricians and orthopaedic surgeons, as well as plastic surgeons and MSAC considered it appropriate to allow access to all eligible medical specialists.

MSAC recalled its preference for agnostic MBS items. However, Botox®, Dysport® and Xeomin® are Section 100 access products. Under the *National Health Act 1953*, such products must be specified in MBS descriptors, meaning an agnostic approach is not appropriate for these MBS items.

MSAC considered that as practice varies, and there are no frequency restrictions between injections in the corresponding PBS listings nor the existing MBS items, MSAC recommended that there should be no frequency restriction for Xeomin® injections.

Regarding the financial impact, MSAC noted that Xeomin® would replace Botox® at a 1:1 ratio (dosage units), so the net impact to the MBS would be neutral. MSAC considered it unlikely that cost saving would be realised if Dysport® is replaced by Xeomin® at a 2.5:1 ratio given the small market share of Dysport®.

MSAC supported amending MBS items 18354 and 18361 to include Xeomin® as MSAC considered the injection to be safe and effective, with minimal economic and financial impact.

4. Background

This is the first time that MSAC considered Xeomin® for treatment of CP associated spasticity. MSAC has previously considered and recommended injection services for Xeomin® in other clinical indications (Application 1379 – IncobotulinumtoxinA, injection of, for blepharospasm, cervical dystonia (spasmodic torticollis) and post-stroke spasticity of the upper limb) and are currently listed on the MBS alongside comparators Botox® and Dysport® (MBS Items: 18353, 18365, 18369, and 18374). MSAC also supported Xeomin® for treatment of chronic sialorrhea in its April 2025 meeting (Application 1800), but it is not yet listed on the schedule.

Xeomin® consists of a white to off-white powder for solution for injection. Each vial of Xeomin® powder for solution for injection contains 50 or 100 units of incobotulinumtoxinA. Xeomin® is reconstituted prior to use with sodium chloride 9 mg/mL (0.9%) solution for injection. Reconstituted Xeomin® is injected intraglandularly using a suitable sterile needle (e.g. 27-30 gauge/0.30-0.40 mm diameter/12.5 mm length).

Injections can only be delivered once every 12 weeks.

Neurologists, rehabilitation specialists, paediatricians, and orthopaedic surgeons provide the service to both adult and paediatric populations, in addition to plastic surgeons for the adult population.

Merz Australia provide training workshops throughout the year in injections and ultrasound use with the aid of a sonographer. Workshops are provided for a range of existing indications which Xeomin® treats.

5. Prerequisites to implementation of any funding advice

Xeomin® was first registered on the Australian Register of Therapeutic Goods (ARTG: ID 205508) on the 21st of March 2014. It is indicated for the symptomatic treatment of spasticity of the lower and/or upper limbs in children and adolescents aged 2 to 17 years, as well as spasticity of the upper limb in adults. In May 2025 the approved Product Information (PI) was updated to include treatment of spasticity of the lower limb affecting the ankle joint in adults as well[1].

[1] Australian Register of Therapeutic Goods – Xeomin – Product Information template

6. Proposal for public funding

The amendment of existing MBS items 18354 and 18361 is requested to utilise Xeomin® injection services for lower-limb (Table 1) and upper-limb (Table 2) spasticity associated with CP in patients 2 years and older. The inclusion of Xeomin® is the only amendment necessary, with all other details of the service (including the fee) remaining unchanged.

Table 1 Amendment of MBS Item 18354 to include incobotulinumtoxinA (Xeomin) for treatment of cerebral palsy lower-limb spasticity

Category 3 – THERAPEUTIC PROCEDURES
MBS item 18354 Botulinum Toxin Type A Purified Neurot~~i~~oxin Complex (Botox), Clostridium Botulinum Type A Toxin-Haemagglutinin Complex (Dysport), **or incobotulinumtoxinA (Xeomin)**, injection of, for the treatment of dynamic equinus foot deformity (including equinovarus and equinovalgus) due to spasticity in an ambulant cerebral palsy patient, if: (a) the patient is at least 2 years of age; and (b) the treatment is for all or any of the muscles subserving one functional activity and supplied by one motor nerve, with a maximum of 4 sets of injections for the patient on any one day (with a maximum of 2 sets of injections for each lower limb), including all injections per set (Anaes.)
Fee: $142.25 Benefit: 75% = $106.70 85% = $120.95[2]

Typographical error corrected in ~~strikethrough text~~ and *italics*

Table 2 Amendment of MBS Item 18361 to include incobotulinumtoxinA (Xeomin) for treatment of cerebral palsy upper-limb spasticity

Category 3 – THERAPEUTIC PROCEDURES
MBS item 18361 Clostridium Botulinum Type A Toxin-Haemagglutinin Complex (Dysport), Botulinum Toxin Type A Purified Neurotoxin Complex (Botox), **or incobotulinumtoxinA (Xeomin)**, injection of, for the treatment of moderate to severe upper limb spasticity due to cerebral palsy if: (a) the patient is at least 2 years of age; and (b) the treatment is for all or any of the muscles subserving one functional activity and supplied by one motor nerve, with a maximum of 4 sets of injections for the patient on any one day (with a maximum of 2 sets of injections for each upper limb), including all injections per set (Anaes.)
Fee: $142.25 Benefit: 75% = $106.70 85% = $120.95[3]

[2] The MBS item 18354 fee at the time of MSAC consideration was $145.65 – see Section 2

[3] The MBS item 18361 fee at the time of MSAC consideration was $146.65 – see Section 2

7. Population

The requested population is patients with cerebral palsy aged 2 years and older with:

- Moderate to severe spasticity of the upper limb.
- Dynamic equinus foot deformity due to spasticity.

CP refers to a group of neurological disorders that appear in infancy or early childhood and permanently affect body movement and muscle coordination. Spasticity, where muscles stiffen or tighten, affects approximately 70–90% of children with the disorder[4,5]. The increased muscle tone due to spasticity results in a limited range of passive and active motion in joints and contributes to development of joint contractures, poor muscular control, and hyperactive reflexes.

Spasticity has been associated with reduced health-related quality of life[6,7] which may be attributed in part to factors such as reduced mobility[8], inability to self-care[9], and pain[10,11,12]. Goals of spasticity treatments include reducing muscle spasms, facilitating mobility and dexterity, improving patient ease of care as well as hygiene/selfcare, facilitating brace use, improving posture, minimizing contractures and deformity as well as reducing pain.

8. Comparator

Botox® is the nominated comparator as it is the market leading injectable toxin for the indications sought and has a 1:1 dose equivalence with Xeomin®.

The pattern of substitution will be partial as in some cases, Xeomin® would replace the use of the comparator, but not all. Botox® would be substituted at the uptake rate for Xeomin®, which is redacted% in year 1, redacted% in year 2, and redacted% in years 3 and 4. The vast majority of the substitution would be of Botox®, but a small fraction of Dysport® may also be substituted.

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[4] HÄGGLUND, G. & WAGNER, P. 2008. Development of spasticity with age in a total population of children with cerebral palsy. *BMC Musculoskelet Disord,* 9, 150

[5] CANS, C. 2000. Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. 42, 816-824

[6] COLVER, A., RAPP, M., EISEMANN, N., EHLINGER, V., THYEN, U., DICKINSON, H. O., PARKES, J., PARKINSON, K., NYSTRAND, M., FAUCONNIER, J., MARCELLI, M., MICHELSEN, S. I. & ARNAUD, C. 2015. Self-reported quality of life of adolescents with cerebral palsy: a cross-sectional and longitudinal analysis. *Lancet,* 385, 705-16

[7] PARK, E. Y. 2018. Path analysis of strength, spasticity, gross motor function, and health-related quality of life in children with spastic cerebral palsy. *Health Qual Life Outcomes,* 16, 70

[8] AKODU, A. K., OLUWALE, O. A., ADEGOKE, Z. O., AHMED, U. A. & AKINOLA, T. O. 2012. Relationship between spasticity and health related quality of life in individuals with cerebral palsy. *Nig Q J Hosp Med,* 22, 99-102.

[9] ÖHRVALL, A. M., ELIASSON, A. C., LÖWING, K., ÖDMAN, P. & KRUMLINDE-SUNDHOLM, L. 2010. Self-care and mobility skills in children with cerebral palsy, related to their manual ability and gross motor function classifications. *Dev Med Child Neurol,* 52, 1048-55.

[10] GEISTER, T. L., QUINTANAR-SOLARES, M., MARTIN, M., AUFHAMMER, S. & ASMUS, F. 2014. Qualitative development of the 'Questionnaire on Pain caused by Spasticity (QPS),' a pediatric patient-reported outcome for spasticity-related pain in cerebral palsy. *Qual Life Res,* 23, 887-96.

[11] POIROT, I., LAUDY, V., RABILLOUD, M., ROCHE, S., GINHOUX, T., KASSAÏ, B. & VUILLEROT, C. 2017. Prevalence of pain in 240 non-ambulatory children with severe cerebral palsy. *Ann Phys Rehabil Med,* 60, 371-375

[12] PENNER, M., XIE, W. Y., BINEPAL, N., SWITZER, L. & FEHLINGS, D. 2013. Characteristics of pain in children and youth with cerebral palsy. *Pediatrics,* 132, e407-13.

9. Summary of public consultation input

Consultation input was welcomed from:

- Cerebral Palsy Alliance (CPA)
- Rehabilitation Medicine Society of Australia and New Zealand (RMSANZ).

Level of support for public funding

Both CPA and RMSANZ expressed support at the public funding of this application.

Comments on PICO

- CPA noted adding Xeomin® to the existing MBS items for botulinum toxin as appropriate, and agreed with the proposed population to include adults as well as children. RMSANZ noted the proposed eligibility criteria and population as appropriate.
- CPA noted that the proposed approach to delivery is in line with current practice. RMSANZ agreed, and suggested that delivery of this service be limited to specialists trained in spasticity assessment and management technique. RMSANZ also noted a maximum of 4 episodes of injections within one year, and suggested that, where appropriate, multidisciplinary rehabilitation should be available to maximise the benefits associated with injections.
- Both CPA and RMSANZ agreed with the proposed comparator, with RMSANZ noting the comparator meets the standard of care, captures current practice, is applicable for all areas and populations, and is effective in practice.
- Both CPA and RMSANZ agreed with proposed outcomes, with RMSANZ noting no concerns about the sustainability of proposed outcomes and no other potential outcomes anticipated.
- CPA noted the proposed item descriptors as broadly appropriate, outlining that MBS 18354 is 'somewhat restrictive' as it excludes those who have non-ambulant CP. RMSANZ noted the descriptor limits the use to specialists trained in and involved in the management of the individual with CP, and defines patient access and suitability. RMSANZ noted clinical practice recommends Xeomin® is able to be accessed a maximum of 4 times a year, instead of 3 as proposed.
- CPA supported the proposed fee, and RMSANZ noted it is consistent with similar health services and technologies. RMSANZ also stated that decisions regarding out-of-pocket expenses remains the responsibility of the providing medical practitioner.

Support for Implementation and Issues

- RMSANZ expressed its support for the implementation of Xeomin® into the management of spasticity related to CP, noting that any potential barriers can be easily addressed by following the same protocols associated with Botulinum Toxin A treatment.
- RMSANZ noted that training for specialties are available, and highlighted that data collection can be undertaken as part of the medical practitioner's Continuing Professional Development (CPD) program and accreditation requirements.

10. Characteristics of the evidence base

The evidence base for the safety and efficacy of Xeomin® has been established in paediatric populations with CP however, CP does not stop at adulthood. Knowing this, the PBAC has previously shown pragmatism by recommending Botox® and Dysport® for treatment in adult CP patients as well, despite their respective trials being conducted exclusively in paediatric populations.

Two (2) pivotal trials demonstrated the safety and efficacy of Xeomin® in the treatment of upper and lower limb spasticity in children and adolescents (aged 2-17 years) with CP[13,14]. *(Heinen et al., 2021) (Dabrowski et al., 2021)* As the use of placebo in this vulnerable age group is considered unethical and unfeasible, clinical efficacy and safety is presented against low-dose Xeomin® as a proxy for placebo. Long term follow-up data was provided in the TIMO study[15] *(Kaňovský et al., 2022)* and the open label extension period (OLEX) in XARA.

No double-blinded randomised controlled trials (RCT) providing direct comparative evidence between Xeomin® and Botox® have been conducted. Study R-201212 an open-label comparative study with Botox®[16] *(Kurenkov et al., 2017)* was included in the PBAC submission as supporting evidence for equivalence between Xeomin® and Botox® in the treatment of dynamic equinus foot deformity in children with CP. These studies are outlined in Table 3.

[13] DABROWSKI, E., CHAMBERS, H. G., GAEBLER-SPIRA, D., BANACH, M., KAŇOVSKÝ, P., DERSCH, H., ALTHAUS, M., GEISTER, T. L. & HEINEN, F. 2021. IncobotulinumtoxinA efficacy/safety in upper-limb spasticity in pediatric cerebral palsy: Randomized controlled trial. *Pediatric neurology,* 123**,** 10-20.

[14] HEINEN, F., KANOVSKÝ, P., SCHROEDER, A. S., CHAMBERS, H. G., DABROWSKI, E., GEISTER, T. L., HANSCHMANN, A., MARTINEZ-TORRES, F. J., PULTE, I. & BANACH, M. 2021. IncobotulinumtoxinA for the treatment of lower-limb spasticity in children and adolescents with cerebral palsy: A phase 3 study. *Journal of pediatric rehabilitation medicine,* 14**,** 183-197

[15] KAŇOVSKÝ, P., HEINEN, F., SCHROEDER, A. S., CHAMBERS, H. G., DABROWSKI, E., GEISTER, T. L., HANSCHMANN, A., MARTINEZ-TORRES, F. J., PULTE, I. & BANACH, M. 2022. Safety and efficacy of repeat long-term incobotulinumtoxinA treatment for lower limb or combined upper/lower limb spasticity in children with cerebral palsy. *Journal of pediatric rehabilitation medicine,* 15**,** 113-127

[16] KURENKOV, A. L., KLOCHKOVA, O. A., BURSAGOVA, B. I., KARIMOVA, H. M., KUZENKOVA, L. M., MAMEDYAROV, A. M., NAMAZOVA-BARANOVA, L. S., AGRANOVICH, O. V., AGRANOVICH, A. O., SOBOLEVA, O. A., KHAPAEVA, M. M., BATYSHEVA, T. T. & SARZHINA, M. N. 2017. [Efficacy and safety of botulinum toxin type A (IncobotulinumtoxinA) in the treatment of patients with cerebral palsy]. *Zh Nevrol Psikhiatr Im S S Korsakova,* 117**,** 37-44.

Table 3 Key features of the clinical evidence for incobotulinumtoxinA (Xeomin®) for CP spasticity

References	Design/duration	Risk of bias	Patient population	Outcome(s)
TIM (Treatment with IncobotulinumtoxinA in Movement)	Phase III, randomised, double-blind, parallel-group, dose-response trial. 26 to 74 weeks.	*Low*	Children and adolescents (n=311) with lower-limb spasticity due to cerebral palsy randomised 1:1:2 to three parallel Xeomin dose groups (low, mid or high).	*Efficacy:* AS-PF, GICS-PF, GMFM *Safety:* AEs
TIMO (Treatment with IncobotulinumtoxinA in Movement Open-Label)	Open-label, non-controlled, long-term study 48 to 64 weeks	*Moderate*	The study included children and adolescents with lower limb spasticity from the TIM pivotal trial (n = 124) as well as new recruits with upper and/or lower limb spasticity due to cerebral palsy (n = 246).	*As above*
XARA (IncobotulinumtoxinA in Arm Treatment in Cerebral Palsy)	Phase III, randomised, double-blind, parallel-group, dose-response trial MP – 16 weeks EP – 48 weeks	*Low*	Children and adolescents (n=351) with upper and/or lower limb spasticity due to cerebral palsy randomised 1:1:2 to three parallel Xeomin dose groups (low, mid or high).	*Efficacy:* AS, GICS, GMFM *Safety:* AEs
Study R-201212	Open-label, randomised, comparative study. 12 weeks.	*Moderate*	Children (n=64) with spastic equinus and equinovarus foot deformity due to cerebral palsy randomised 1:1 to Xeomin or Botox.	*Efficacy:* AS-PF *Safety:* AEs

AS-PF, Ashworth Scale of Plantar Flexors; GICS-PF, Global Impression of Change Scale of Plantar Flexors, AS, Ashworth Scale; GICS, Global Impression of Change Scale; GMFM, gross motor function measure; MP, main period; EP, extension period.

A naïve indirect comparison was included in the PBAC submission as formal statistical analyses were considered inappropriate due to the heterogeneity between studies and the poor quality of reporting in the historical Botox studies.

As Study R-201212 – a small, open-label study in the lower-limb population – was the only comparative study between Xeomin® and Botox®, an indirect comparison was made. However, this proved difficult due to the poor quality of the historical Botox studies. Transparent information on interventions, observations, and reporting outcomes were largely missing from the comparator trials, as well as containing small and poorly defined populations.

The Botox studies while not placebo controlled,[17] did contain treatment arms without pharmaceutical intervention, and therefore an assumption was made that the low-dose treatment arms in the Xeomin® trials function as a common "no intervention" comparator. Table 4 outlines the Botox studies used in the naïve comparison between treatments.

[17] Fehlings (2000) defined ethical objections to placebo injections, and Russo (2007) described the requirement for general anaesthesic as the reason to exclude placebo injections.

Table 4 Overview of Botox studies used in indirect comparison

Study ID	Study type	Population	Treatments	Comparative Outcomes
Flett et al. 1999	Single-blind, randomized, controlled trial	n = 20, 2-8 years with CP and muscle spasticity of the lower extremity	Botox, dosage 4–8 U/kg and maximum of 20 units per site vs fixed plaster casting for 4 weeks	MAS, range of movement scores, GMFM scores, total PRS scores and GSS scores.
Fehlings et al. 2000	*As above.*	30 children, hemiplegic CP, 2.5-10 years	Botox (2 to 6 U/kg) + OT (n=14), OT alone (n=15)	Modified Ashworth Scale.
Lowe et al. 2006	*As above.*	42 children, 2-8 years, CP hemiplegic, at least 2 on Ashworth scale	Botox (max dose 8 U/kg) + OT (n=21), vs OT alone (n=21).	Ashworth scale (1, 3, 6 months), Adverse events
Russo et al. 2007	*As above.*	43 children, hemiplegic CP, 3-16 years, MAS of at least 2	Botox (12 u/kg) + OT (n=21), OT alone (n=22).	Modified Ashworth Scale, Safety

CP, cerebral palsy; U, units; OT, occupational therapy; MAS, modified Ashworth scale; GMFM, gross motor function measure; PRS, physician rating scale; global scoring scale.

11. Comparative safety and efficacy

Clinical studies of Xeomin®

The phase 3 clinical trials showed that in a paediatric population with CP, treatment with Xeomin® offered significant and consistent improvement in muscle tone and motor function for children with CP spasticity in lower and/or upper limb(s).

The TIM study showed a positive and clinically meaningful treatment response in all treatment groups at Week 4 after injection in the pes equinus as demonstrated by the Ashworth scale (AS) score and global impression of change scale in plantar flexors (GICS-PF) score assessment. The results also indicate a favourable safety and tolerability profile at doses of up to 16 U/kg (maximum 400 U) for patients in all GMFCS severity groups. Long-term efficacy of up to 4 injections of Xeomin® was clearly and consistently demonstrated in TIMO and correspond well to the results of the lead-in study.

Xeomin® treatment was generally well tolerated over both injection cycles, with treatment emergent adverse events (TEAEs) reported in 42.8% of patients overall. The overall incidences of TEAEs and treatment-related TEAEs were higher in the high dose group (49.4% and 7.1%) than in the mid dose group (33.8% and 2.6%) and the low dose group (38.5% and 2.6%). TEAEs assessed by investigators as treatment-related included muscular weakness (n = 5 patients), injection-site pain (n = 4 patients), injection site erythema, pain in an extremity, pyrexia (n = 2 patients each), fall, hematoma, influenza-like illness, injection-site inflammation, injection-site warmth, and rash (n = 1 patient each).

No new or unexpected safety concerns were identified in TIMO and overall, Xeomin treatments were well-tolerated, as evidenced by a very small proportion (1.1%) of study discontinuations due to AEs.

The XARA study showed significant and clinically meaningful improvements from baseline in AS scores at Week 4 in all dose groups. Observed benefits in the treatment of upper-limb as well as lower-limb spasticity are further supported by AS, global, pain-related, and functional efficacy outcomes. Moreover, sustained and consistent spasticity improvements were observed in all outcomes over time with three further treatment cycles with the highest Xeomin® dose in the open label extension (OLEX).

A favourable safety/tolerability profile was observed, with similarly high retention rates when compared with TIM/TIMO. Overall, TEAEs were experienced by 34.4% of subjects (144 of 331

subjects) in the OLEX. The incidence of TEAEs did not increase with further treatment cycles. AEs assessed as treatment-related (5 in total) were AEs of special interest (potentially indicating toxin spread) including mild hypotonia and moderate eyelid ptosis in one patient each in OLEX cycle 1, mild dysphagia and serious AE of moderate influenza-like illness in one patient each in cycle 2, and mild pain in the extremity in one patient in cycle 3. Five subjects in the OLEX discontinued due to TEAEs, two were assessed as related to treatment (eyelid ptosis and influenza like illness). There were no fatal adverse events.

Comparative safety between Xeomin® and Botox®

In Study R-201212 safety was comparable between the treatment groups, with 4 events in 3 patients (9.4%) seen in the Xeomin® group and 2 events in 2 patients (6.3%) seen in the Botox® group. All AEs were mild to moderate, and all events resolved. No study discontinuations in either treatment group were due to adverse events.

AEs were poorly reported, if at all, in the comparator Botox studies. AEs were not reported at all in Flett (1999). Adverse events were briefly mentioned in excluded studies Eames (1999) and Koman (1994). In both studies, patients receiving botulinum toxin injections (Koman [1-2 U/kg BW], n=6; Eames [8-10 U/kg BW], n=27), reported pain at the injection site, n=3 in Koman (1994) and n=1 in Eames (1999). Eames (1999) also described one patient who experienced increased “tripping” following botulinum toxin injection. In the placebo group in Koman (1994) (n=6), pain at the injection site was also reported (n=3), as well as unsteadiness (n=2), fatigue (n=1) and headache (n=1).

Safety outcomes were not detailed in Fehlings (2000) and Lowe (2006). In Russo (2007) a total of 23 AEs were reported in the Botox group, including one SAE. Most AEs were related to use of anaesthetic, but 5 children (23.8%) experienced weakness in the injected limb. No minor AEs were reported in the control group.

Comparative efficacy between Xeomin® and Botox®

The indicative comparative efficacy of Xeomin® compared to Botox® was also supported in the R-201212 study. No significant differences were seen between groups in the treatment with spastic equinus or equinovarus foot deformation. The modified AS score at baseline was 2.6 ± 0.49 in group I (Xeomin) and 2.4 ± 0.56 in group II (Botox). There were no statistically significant differences between groups ($p = 0.207$). Change from baseline in modified AS was maintained over the course of the study (Visit 3, Visit 4) with no differences between treatment groups.

Comparable lower-limb efficacy outcomes with Botox® are outlined in Table 5. At baseline, participants AS/MAS and GMFM scores were similar between TIM and Flett (1999). Both studies reported improvements in AS/MAS scores at 8 weeks vs baseline and improvements were of similar magnitude between both studies. GMFM scores also improved following the first injection cycle in both studies (only one cycle in Flett). A greater improvement was seen in Flett (1999, however, GMFM was measured differently in the studies making a proper comparison between the results impossible. Furthermore, additional therapies were permitted 2 months post injection in the Flett study which may have contributed to the disparity in GMFM results.

Table 5 Comparative outcomes of Xeomin® and Botox® studies for lower-limb CP spasticity

Trial	Dosage	Baseline AS/MAS Mean (SD)	Change in AS/MAS score at 8 weeks vs baseline	Baseline GMFM Mean (SD)	Change in GMFM score at end of IC1 vs baseline
TIM (LS-Mean [SE]; [95% CI])	Low dose (4 U/kg BW), n=156	2.8 (0.5)	-0.69 (0.080); (-0.85; -0.53)	55.7 (20.7)	1.64 (0.392); (0.87; 2.41)[a]
	Mid dose (12 U/kg BW), n=77	2.7 (0.5)	-0.74 (0.088); (-0.91; -0.56)	57.8 (18.5)	1.14 (0.448); (0.25; 2.03) [a]
	High dose (16 U/kg BW), n=78	2.7 (0.6)	-0.62 (0.059); (-0.73; -0.50)	56.3 (18.6)	1.23 (0.288); (0.66; 1.80) [a]
Flett *et al.*, 1999 (Mean)	4–8 U/kg BW, n= 10	Assessed by physio: 2.41 (0.65) Assessed by doctor: 2.69 (0.75)	Assessed by Physio: -1.01 Assessed by Doctor: -1.29	Standing: 55.75 (24.20) Dynamic: 40.61 (24.00)	Standing: 6.8[b] Dynamic: 8.84[b]

Abbreviations: AS, Ashworth scale; MAS, modified Ashworth scale; GMFM, Gross motor function measure, U, unit; BW, body weight. [a] Assessed at 36 weeks [b] Assessed at 6 months

Change in AS/MAS scores as reported in the upper-limb spasticity studies are seen in Table 6. The subjects in XARA and those in the Botox studies are similar in terms of baseline spasticity as measured by AS/MAS, with those in XARA tending to have slightly higher average scores. Reductions in AS/MAS at four weeks/one month were nominally higher in XARA which may be as a result of higher disability in the population. As expected with the way botulinum toxin treatments efficacy wanes over time, the change in AS score was reduced at 14 weeks in XARA. The AS/MAS changes in the Botox studies were more consistent over the observation periods, but may be as a result of small population sizes and or poorly reported differences in treatment,

Exposure to treatment was poorly reported. Lowe (2006) indicated that patients received a single injection over the entire 6-month observation period, which is contrary to clinical practice. It is unclear if the dosing patterns in Fehlings (2000) and Russo (2007) reflect optimal use.

Table 6 Comparative outcomes of Xeomin® and Botox® studies for upper-limb CP spasticity

Trial	Dosage	Baseline AS/MAS Mean (SD)	Change in AS/MAS score vs baseline, first measure [a]	Change in AS/MAS score vs baseline, second measure [b]
XARA (LS-Mean [SE]; [95% CI])	Low dose (2 U/kg BW), n=85	2.6 (0.52)	-0.93 (0.078); (-1.08; -0.78)	-0.4 (0.56)
	Mid dose (6 U/kg BW), n=87	2.6 (0.52)	-1.02 (0.082)	-0.4 (0.56)
	High dose (8 U/kg BW), n=173	2.7 (0.56)	-1.15 (0.056); (-1.26; -1.04)	-0.4 (0.63)
Fehlings et al. 2000 Mean (SD)	No intervention n=14	2.2 (0.59)	-0.26 (0.53)	-0.30 (0.49)
	Botox n=15	2.3 (0.75)	-0.34 (0.45)	-0.29 (0.41)
Lowe et al. 2006 Mean (SD)	No intervention n=21	2.2 (0.1)	-0.03 (NR)	-0.15 (NR)
	Botox n=21	2.4 (0.1)	-1.1 (NR)	-0.8 (NR)
Russo et al. 2007 Mean (SD)	No intervention n=22	2 (NR)	NR	2 (NR)
	Botox n=21	2 (NR)	NR	-1 (NR)

Abbreviations: AS, Ashworth scale; MAS, modified Ashworth scale; U, unit; BW, body weight, NR; not reported. a=four weeks for Xeomin study, one month for Botox, b=14 weeks for Xeomin study, 3 months for Botox.

Clinical claim

When the available evidence is taken as a whole, and when contextualised within Australian clinical practices using botulinum toxins interchangeably for listed applications, the pragmatic therapeutic conclusions are:

- Xeomin® is non-inferior to Botox® in terms of safety in patients 2 years and older with upper or lower limb spasticity due to CP.
- Xeomin® is non-inferior to Botox® in terms of efficacy in patients 2 years and older with upper or lower limb spasticity due to CP.

12. Economic evaluation

A cost-minimisation economic evaluation compared Xeomin® against the main comparator Botox®.

13. Financial/budgetary impacts

The requested PBS listing of Xeomin® for the symptomatic treatment of spasticity would not change the current clinical management algorithm for treatment of upper limb or lower limb spasticity in patients 2 years and older with CP. Xeomin® is not expected to impact the prevalence of the disease, so the market is not expected to grow after listing. Xeomin® would provide an alternate option for clinicians and patients to the currently listed botulinum toxin treatments. Therefore, Xeomin® would not increase the MBS utilisation of items 18354 and 18361, as these items would still be claimed regardless of the prescribed PBS treatment.

In Table 7 the applicant has assumed a rate of displacement by Xeomin® based on their own general commercial experience, with the market share of Xeomin® steadily increasing over the first 6 years of listing.

Xeomin® is expected to replace Botox® in practice at a 1:1 equi-effective dose, resulting in total cost and utilisation neutrality for both the PBS and MBS. However, the equi-effective dose for Xeomin® and Dysport® is expected to be 1:2.5. This means that for every patient switching from Dysport® to Xeomin®, the total PBS services will reduce by a ratio of 2.5 to 1. As a result of this, there would be a reduction of the overall utilisation of MBS items 18354 and 18361 if patients switch to Xeomin® from Dysport®, reducing the cost to the MBS. Dysport®, however, only accounts for 7% of the total market for these indications, so the number of patients switching to Xeomin® would be low and the resultant cost reduction to the MBS would also be minimal.

Table 7. Xeomin displacement rates

Brand name, molecule name	2025	2026	2027	2028	2029	2030
Xeomin, incobotulinumtoxinA	**Redacted**%[18]	**Redacted** %	**Redacted** %	**Redacted** %	**Redacted** %	**Redacted** %

Table 8 shows the total number of Xeomin® PBS services projected to be dispensed in the six-year period, with <500[18] in 2025 and 500 to <5000 in 2030.

Table 8. Estimated Xeomin PBS services

Brand name, molecule name	2025	2026	2027	2028	2029	2030
Xeomin / IncobotulinumtoxinA - Dynamic equinus foot deformity	**Redacted**[1,18]	**Redacted**[1]	**Redacted**[1]	**Redacted**[1]	**Redacted**[1]	**Redacted**[2]
Xeomin / IncobotulinumtoxinA - Moderate to severe spasticity of the upper limb	**Redacted**[1,18]	**Redacted**[1]	**Redacted**[1]	**Redacted**[1]	**Redacted**[1]	**Redacted**[1]
Total	**Redacted**[1,18]	**Redacted**[1]	**Redacted**[1]	**Redacted**[2]	**Redacted**[2]	**Redacted**[2]

The **redacted** values correspond to the following ranges
1 <500
2 500 to <5000

The administration of Xeomin® is proposed to be listed under the same MBS services used for the current administration of Botox® and Dysport® for the same indications. Xeomin® would replace Botox® at a 1:1 ratio and as such the net impact to the MBS will be neutral. Since Dysport® would be placed by Xeomin® at a 2.5:1 ratio, the net MBS services would decrease slightly. Table 9 shows the estimated net cost to the MBS of listing Xeomin® based on the MBS item fee of $142.25.

[18] Corrected by applicant prior to MSAC consideration

Table 9. Financial impact of Xeomin® on MBS

	2025	2026	2027	2028	2029	2030	Total
Increased cost to MBS	**Redacted**[1,19]	**Redacted**[1]	**Redacted**[1]	**Redacted**[1]	**Redacted**[1]	**Redacted**[1]	**Redacted**[1]
Decreased cost to MBS	-**Redacted**[1,19]	-**Redacted**[1]	-**Redacted**[1]	-**Redacted**[1]	-**Redacted**[1]	-**Redacted**[1]	-**Redacted**[1]
Net cost to the MBS	-**Redacted**[1,19]	-**Redacted**[1]	-**Redacted**[1]	-**Redacted**[1]	-**Redacted**[1]	-**Redacted**[1]	-**Redacted**[1]

The **redacted** values correspond to the following ranges
1 $0 to <$10 million

14. Other relevant information

Nil.

15. Applicant comments on MSAC's Public Summary Document

The applicant had no comment.

16. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website

[19] Corrected by applicant prior to MSAC consideration