MSAC Application

MSAC Application for Submission for Xeomin (incobotulinumtoxinA) for treatment of lower limb spasticity following an acute event

PICO Set

Population

Describe the population in which the proposed health technology is intended to be used:

Adults with moderate to severe spasticity of the lower-limb following an acute event.

This event may be a clinical or external event that leads to upper motor neuron lesions resulting in spasticity for example stroke, traumatic brain injury, spinal cord injury, infection or hypoxia.

Specify any characteristics of patients with, or suspected of having, the medical condition, who are proposed to be eligible for the proposed health technology, describing how a patient would be investigated, managed and referred within the Australian healthcare system in the lead up to being considered eligible for the technology:

Stroke is the leading cause of adult disability in Australia. [1] Spasticity typically develops within the first 3-6 months after stroke, though onset can be as early as 1-week after the event. [2] Up to 80% of survivors experience motor impairment, and 20–40% develop spasticity within the first 6 months [3], with symptoms often peaking between 3 and 12 months. [4]

Post-stroke spasticity involving the lower limb most often presents as equinus deformity due to plantar flexor overactivity, causing toe-walking, knee hyperextension, and impaired balance, [5] and is present in almost 1 in 5 stroke survivors. [6] The resulting abnormal gait patterns include equinovarus deformity, stiff-knee gait, and scissoring gait, which increase fall risk and energy expenditure during walking. [4]

The diagnosis of lower-limb spasticity following stroke requires a multidisciplinary approach assessing motor power, range of motion, and muscle tone. Deformities such as dynamic equinus are identified and standardised tools are used to assess functional impairment. The Modified Ashworth Scale (MAS) is the most universally accepted clinical tool used to measure an increase in muscle tone in a range of other spasticity inducing aetiologies such as brain injury and stroke. [7]

Table 1 shows how the MAS grades muscle resistance to passive movement on a 6-point ordinal scale, with scores 2 and greater considered as indicating moderate to severe spasticity. [8] The MAS increased sensitivity of the original Ashworth Scale by introducing the 1+ score.

Table 1 Modified Ashworth Scale of Muscle Tone

Ashworth Scale	Degree of muscle tone
0	No increase in muscle tone
1	Slight increase in muscle tone, with a catch and release or minimal resistance at the end of the range of motion when an affected part(s) is moved in flexion or extension.
1+	Slight increase in muscle tone, manifested as a catch, followed by minimal resistance through the remainder (less than half) of the range of motion.
2	A marked increase in muscle tone throughout most of the range of motion, but affected part(s) are still easily moved
3	Considerable increase in muscle tone, passive movement difficult
4	Affected part(s) rigid in flexion or extension

Provide a rationale for the specifics of the eligible population:

Stroke is the third leading cause of death and a leading cause of disability in Australia and, according to the Australian Stroke Foundation 2023 data, there are over 445,000 stroke survivors living in Australia. In 2024, a total of 45,785 strokes were recorded, comprising 34,793 first-ever strokes and 10,992 recurrent strokes, effectively one stroke every 11 minutes. The crude incidence rate is estimated at 159 per 100,000 population, with an age-standardized rate of 124 events per 100,000 in 2021. [9]

Up to 65% of stroke survivors experience disability requiring assistance with daily activities. [10] Post-stroke spasticity develops in approximately 25-40% of stroke survivors, with lower limb spasticity specifically affecting between 30% [11, 12] and >60% of survivors in Australia. [2] This condition most commonly manifests within the first month following stroke, predominantly affecting ankle plantar flexors and causing equinovarus deformities that significantly impair mobility and quality of life.

Equinus foot deformity is the most common acquired deformity of the lower limb following a stroke. It is characterized by a downward deformity of the ankle, usually associated with an internal rotation of the foot, causing varus-supination. Sometimes, clawed toes are also present, further affecting the physiological anatomy of the foot. [13]

Are there any prerequisite tests?
No

Are the prerequisite tests MBS funded?
N/A

Provide details to fund the prerequisite tests:
N/A

Intervention

Name of the proposed health technology:

IncobotulinumtoxinA (brand name: Xeomin®)

Describe the key components and clinical steps involved in delivering the proposed health technology:

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. A suitable sterile needle should be used for administration.

An injection volume of approximately 0.3 to 1 ml per injection site is recommended when treating spasticity of the lower limb. A reconstituted solution at a concentration of 5 units/0.1 mL should be used. The maximum total dose for the treatment of unilateral spasticity of the lower limb affecting the ankle joint should not exceed 400 units per treatment session.

Table 2 Injection scheme for treatment of lower-limb spasticity with need to treat toe muscles

Target muscle	Units	mL #	No. injection sites #
Gastrocnemius (medial & lateral head)*	75 + 75	1.5 + 1.5	4 – 6
Soleus*	75	1.5	2 – 4
Tibialis posterior*	75	1.5	2 – 3
Flexor digitorum longus*	50	1.0	1 - 3
Flexor hallucis longus*	50	1.0	1 - 2

* In the main period of the pivotal clinical study Injection of all these muscles was mandatory

Maximum 1.0 mL per injection site

Table 3 Injection scheme for treatment of lower-limb spasticity without need to treat toe muscles)

Target muscle	Units	mL #	No. injection sites #
Gastrocnemius (medial & lateral head)*	100 + 100	2.0 + 2.0	4 – 6
Soleus*	100	2.0	2 – 4
Tibialis posterior*	100	2.0	2 – 3

* In the main period of the pivotal clinical study Injection of all these muscles was mandatory

Maximum 1.0 mL per injection site

Identify how the proposed technology achieves the intended patient outcomes:

XEOMIN® blocks cholinergic transmission at the neuromuscular junction by inhibiting the release of acetylcholine from peripheral cholinergic nerve terminals. This inhibition occurs according to the following sequence:

- Heavy chain of toxin binding to cholinergic nerve terminals
- Internalization of the toxin within vesicles into the nerve terminal
- Translocation of the light-chain of the toxin molecule into the cytosol of the nerve terminal
- Enzymatic cleavage of SNAP25, the presynaptic target protein essential for the release of acetylcholine.

Complete recovery of endplate function/impulse transmission after intramuscular injection normally occurs within 3-4 months as nerve terminals sprout and reconnect with the muscle endplate and the presynaptic neurotransmitter release mechanism becomes functional again.

Does the proposed health technology include a registered trademark component with characteristics that distinguishes it from other similar health components?

Yes

Explain whether it is essential to have this trademark component or whether there would be other components that would be suitable:

It is not essential to have the trademarked component and, in this indication, Xeomin can be used interchangeably with other botulinum toxin preparations Botox and Dysport.

Are there any proposed limitations on the provision of the proposed health technology delivered to the patient (For example: accessibility, dosage, quantity, duration or frequency):

Yes – the service can only be delivered once every 12 weeks at most.

Provide details and explain:

N/A

If applicable, advise which health professionals will be needed to provide the proposed health technology:

The proposed health service can be provided by the following specialists:

- Must be treated by a neurologist; OR
- Must be treated by an orthopaedic surgeon; OR
- Must be treated by a rehabilitation specialist; OR
- Must be treated by a plastic surgeon; OR
- Must be treated by a geriatrician.

If applicable, advise whether delivery of the proposed health technology can be delegated to another health professional:

N/A

If applicable, advise if there are any limitations on which health professionals might provide a referral for the proposed health technology:

The service providers will be the service referrers.

Is there specific training or qualifications required to provide or deliver the proposed service, and/or any accreditation requirements to support delivery of the health technology?

Yes

Provide details and explain:

Merz Australia provide training workshops throughout the year in injections and ultrasound use with the aid of a sonographer.

Indicate the proposed setting(s) in which the proposed health technology will be delivered:

☒ Consulting rooms
☐ Day surgery centre
☐ Emergency Department
☒ Inpatient private hospital
☒ Inpatient public hospital
☐ Laboratory
☒ Outpatient clinic
☒ Patient's home
☐ Point of care testing
☐ Residential aged care facility
☐ Other (please specify)

Is the proposed health technology intended to be entirely rendered inside Australia?

Yes

Provide additional details on the proposed health technology to be rendered outside of Australia:

N/A

Comparator

Nominate the appropriate comparator(s) for the proposed medical service (i.e., how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian healthcare system). This includes identifying healthcare resources that are needed to be delivered at the same time as the comparator service:

Botulinum toxin type A (BOTOX®)

List any existing MBS item numbers that are relevant for the nominated comparators:

18360

Provide a rationale for why this is a comparator:

Botox is the nominated comparator as it is the market leading injectable toxin for the indication/s sought and has a 1:1 dose equivalence with incobotulinumtoxinA (XEOMIN®).

Pattern of substitution – Will the proposed health technology wholly replace the proposed comparator, partially replace the proposed comparator, displace the proposed comparator or be used in combination with the proposed comparator?

☐ None (used with the comparator)
☐ Displaced (comparator will likely be used following the proposed technology in some patients)
☒ Partial (in some cases, the proposed technology will replace the use of the comparator, but not all)
☐ Full (subjects who receive the proposed intervention will not receive the comparator)

Outline and explain the extent to which the current comparator is expected to be substituted:

The comparator is estimated to be substituted at the uptake rate for Xeomin, which is 2.5% in year 1, 5% in year 2, and 10% in years 3 and 4. The vast majority of the substitution will be of Botox, but a small fraction of Dysport may also be substituted.

Outcomes

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

☒ Health benefits
☒ Health harms
☐ Resources
☐ Value of knowing

Outcome description – include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

Treatment with incobotulinumtoxinA (Xeomin) results in non-inferior health outcomes when compared to Botox. Health benefits evaluated in the clinical trial evidence include:

- Quantitative measures of spasticity using the Modified Ashworth Scale

Health harms evaluated include:

- Incidence of treatment emergent AEs (TEAEs), TEAEs of special interest, (TEAESIs) and serious TEAEs.

Proposed MBS items

How is the technology/service funded at present? (e.g., research funding; State-based funding; self-funded by patients; no funding or payments):

Self-funded by patients.

Provide at least one proposed item with their descriptor and associated costs, for each Population/Intervention:

MBS item number (where used as a template for the proposed item)	18360
Category number	Category 3
Category description	Therapeutic Procedures
Proposed item descriptor	Botulinum Toxin Type A Purified Neurotixin Complex (Botox), or Clostridium Botulinum Type A Toxin-Haemagglutinin Complex (Dysport), **or IncobotulinumtoxinA (Xeomin),** injection of, for the treatment of moderate to severe focal spasticity, if: (a) the patient is at least 18 years of age; and (b) the spasticity is associated with a previously diagnosed neurological disorder; and (c) treatment is provided as: (i) second line therapy when standard treatment for the conditions has failed; or (ii) an adjunct to physical therapy; and (d) 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 limb), including all injections per set; and (e) the treatment is not provided on the same occasion as a service mentioned in item 18365
Proposed MBS fee	$145.65 Benefit: 75% = $109.25 85% = $123.85
Indicate the overall cost per patient of providing the proposed health technology	$145.65
Please specify any anticipated out of pocket expenses	N/A
Provide any further details and explain	N/A

Algorithms

PREPARATION FOR USING THE HEALTH TECHNOLOGY

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, before patients would be eligible for the proposed health technology:

For spasticity management, systematic assessment throughout the first-year post-stroke proves essential given that 13% of cases develop beyond three months and severity increases over the first 12 months. [11, 14] Assessment should occur at one month, three months, six months, and 12 months, with ongoing monitoring for late-developing cases. [15]

In clinical practice, clinicians would complete a physical examination including an assessment of motor function, muscle tone, range of motion, reflexes, limb deformity and anatomical alignment.

For prescribing purposes, a diagnosis of moderate to severe spasticity (using a Modified Ashworth scale score of ≥3) is required for patients to access botulinum toxin treatment for lower limb spasticity following an acute event.

Is there any expectation that the clinical management algorithm before the health technology is used will change due to the introduction of the proposed health technology?

No

Describe and explain any differences in the clinical management algorithm prior to the use of the proposed health technology vs. the comparator health technology:

The listing of Xeomin will not change the current clinical management of patients moderate to severe lower limb spasticity following an acute event.

Xeomin would displace the use of Botox with a 1:1 equi-effective dose.

USE OF THE HEALTH TECHNOLOGY

Explain what other healthcare resources are used in conjunction with delivering the proposed health technology:

N/A

Explain what other healthcare resources are used in conjunction with the comparator health technology:

N/A

Describe and explain any differences in the healthcare resources used in conjunction with the proposed health technology vs. the comparator health technology:

N/A

CLINICAL MANAGEMENT AFTER THE USE OF HEALTH TECHNOLOGY

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the proposed health technology:

The sponsor does not propose any changes to the current clinical management algorithm.

The current clinical management algorithm for adults with moderate to severe spasticity of the lower limb following and acute event is outlined in Figure 1 and reflects the diagnostic/prescribing criteria as previously accepted for Botox and Dysport, as well as current Australian clinical guidelines.

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the comparator health technology:

As described above.

Describe and explain any differences in the healthcare resources used *after* the proposed health technology vs. the comparator health technology:

The listing of Xeomin will not change the current clinical management of patients moderate to severe lower limb spasticity following an acute event.

Xeomin would displace the use of Botox with a 1:1 equi-effective dose.

Insert diagrams demonstrating the clinical management algorithm with and without the proposed health technology:

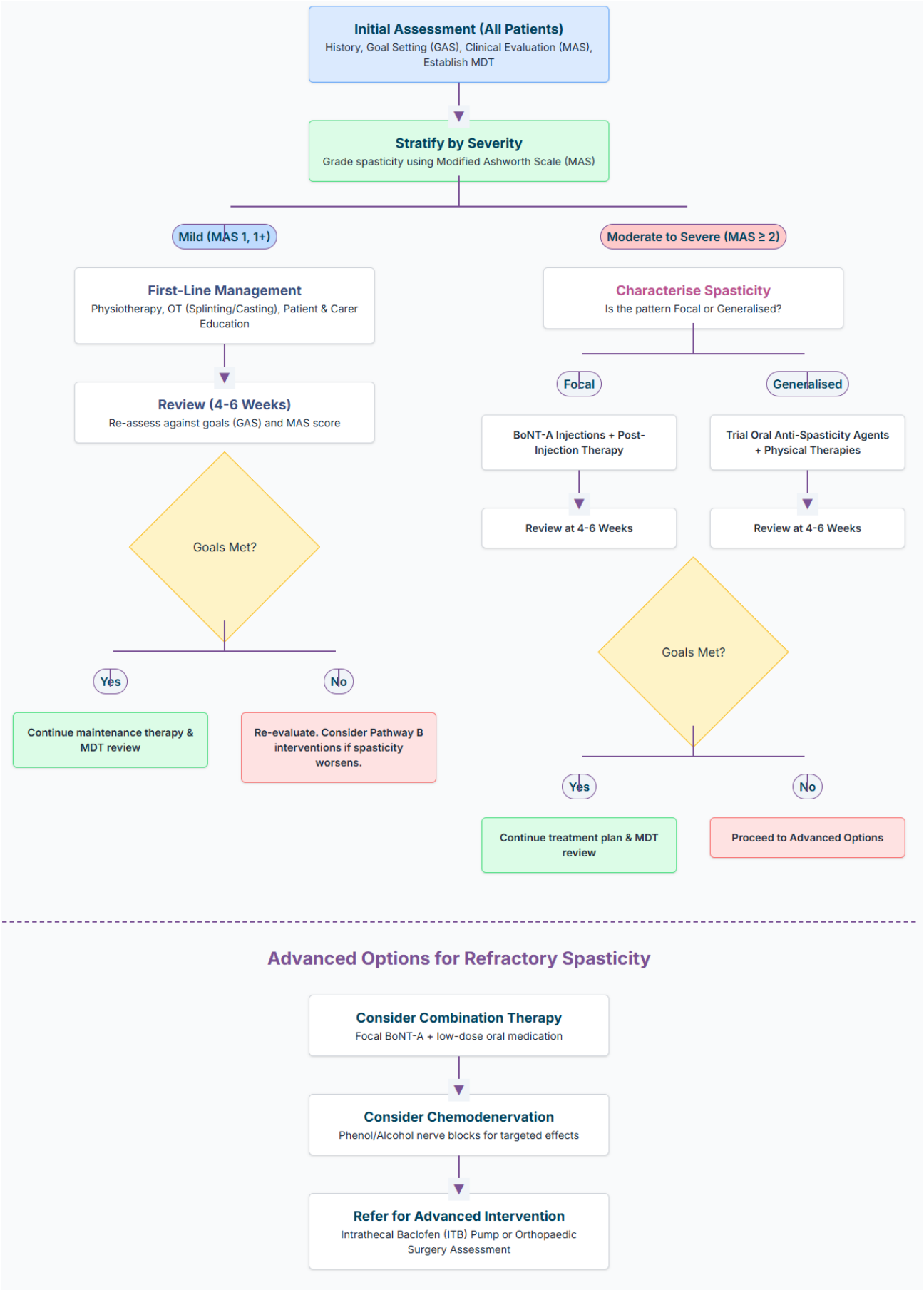

Figure 1. Clinical management algorithm for post-stroke lower-limb spasticity

Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)?

☐ Superior
☒ Non-inferior
☐ Inferior

Please state what the overall claim is, and provide a rationale:

Treatment of lower limb spasticity with incobotulinumtoxinA (Xeomin) following an acute event is non-inferior to Botox with regards to efficacy and safety. This was demonstrated in a randomised controlled trial, J-PLUS, details of which are tabulated in the Summary of Evidence. Results of J-PLUS were compared to Botox study results via an indirect analysis which was provided to the PBAC for review at its March 2026 meeting.

The non-inferiority of Xeomin and Botox has been well-established and accepted by the PBAC, with the products considered equivalent and interchangeable on a patient-level basis. In the public summary document for the most recent consideration of Xeomin in 2019, the PBAC declared that "…BOTOX®, Dysport® and Xeomin®, should be treated as interchangeable on an individual patient basis under Section 101(3BA) of the National Health Act 1953." (6.12 INCOBOTULINUMTOXINA, Public Summary Document, Paragraph 6.16, November 2019 PBAC Meeting). The PBS therapeutic relativity sheets list Xeomin and Botox as having a 1:1 dose equivalence.

Why would the requestor seek to use the proposed investigative technology rather than the comparator(s)?

IncobotulinumtoxinA, is the only botulinum toxin formulation that is a pure botulinumtoxinA formulation, free of accessory proteins.

Identify how the proposed technology achieves the intended patient outcomes:

Xeomin blocks cholinergic transmission at the neuromuscular junction by inhibiting the release of acetylcholine from peripheral cholinergic nerve terminals. This inhibition occurs according to the following sequence:

- heavy chain of toxin binding to cholinergic nerve terminals
- internalization of the toxin within vesicles into the nerve terminal
- translocation of the light-chain of the toxin molecule into the cytosol of the nerve terminal
- enzymatic cleavage of SNAP25, the presynaptic target protein essential for the release of acetylcholine.

Complete recovery of endplate function/impulse transmission after intramuscular injection normally occurs within 3-4 months as nerve terminals sprout and reconnect with the muscle endplate and the presynaptic neurotransmitter release mechanism becomes functional again.

For some people, compared with the comparator(s), does the test information result in:

A change in clinical management? No

A change in health outcome? No

Other benefits? No

Please provide a rationale, and information on other benefits if relevant:

N/A

In terms of the immediate costs of the proposed technology (and immediate cost consequences, such as procedural costs, testing costs etc.), is the proposed technology claimed to be more costly, the same cost or less costly than the comparator?

☐ More costly
☒ Same cost
☐ Less costly

Provide a brief rationale for the claim:

The requested PBS listing of Xeomin for the symptomatic treatment of lower limb spasticity in adults will not change the current clinical management algorithm for this condition. Xeomin is not expected to impact the prevalence of the disease, so the market is not expected to grow after listing. Xeomin will provide an alternate option for clinicians and patients to the currently listed botulinum toxin treatments. Therefore, Xeomin will not increase the MBS utilisation of item 18360, and this item will still be claimed regardless of the prescribed PBS treatment.

In terms of dose relativities, 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, using previous TGA and PBAC determinations, the equi-effective dose for Xeomin and Dysport is expected to be 1:3.75. This means that for every patient switching from Dysport to Xeomin, the total PBS services will reduce by a ratio of 3.75 to 1. As a result of this, there will be a reduction of the overall utilisation of MBS item 18360 and if patients switch to Xeomin from Dysport, reducing the cost to the MBS.

Botox dominates the current market, accounting for over 75% of services in 2024. Therefore, since most patients expected to be treated with Xeomin will switch from Botox, the utilisation of MBS item number 18360 will remain largely unchanged and will not generate any further costs to the MBS.

If your application is in relation to a specific radiopharmaceutical(s) or a set of radiopharmaceuticals, identify whether your clinical claim is dependent on the evidence base of the radiopharmaceutical(s) for which MBS funding is being requested. If your clinical claim is dependent on the evidence base of another radiopharmaceutical product(s), a claim of clinical noninferiority between the radiopharmaceutical products is also required.

N/A

Summary of Evidence

Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology. At 'Application Form lodgement',

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
1.	Phase III, randomised, double-blind, parallel-group, placebo-controlled trial	J-PLUS Masakado, Y., Kagaya, H., Kondo, K., Otaka, Y., Dekundy, A., Hanschmann, A., Geister, T.L. and Kaji, R., 2022. Efficacy and safety of Incobotulinumtoxina in the treatment of lower limb spasticity in Japanese subjects. *Frontiers in Neurology*, *13*, p.832937.	Adults (n=208) with unilateral lower spasticity with equinus foot deformity caused by a stroke, randomised 1:1 to receive incobotulinumtoxinA (400U) or placebo (equivalent volume). Health outcomes and safety evaluated. Subjects who completed the main period and met eligibility criteria for re-injection entered an open-label extension period, during which all subjects received incobotulinumtoxinA 400 U for three additional cycles.	https://pubmed.ncbi.nlm.nih.gov/35370917/	March 2022

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11. Zeng, H., et al., *Prevalence and risk factors for spasticity after stroke: a systematic review and meta-analysis.* Frontiers in neurology, 2021. **11**: p. 616097.
12. Gupta, A.D., et al., *Statement of the Rehabilitation Medicine Society of Australia and New Zealand for the therapeutic use of botulinum toxin A in spasticity management.* Internal medicine journal, 2024. **54**(1): p. 178-182.
13. Campanini, I., et al., *Physical therapy interventions for the correction of equinus foot deformity in post-stroke patients with triceps spasticity: A scoping review.* Frontiers in neurology, 2022. **13**: p. 1026850.
14. Nam, K.E., et al., *When does spasticity in the upper limb develop after a first stroke? A nationwide observational study on 861 stroke patients.* Journal of Clinical Neuroscience, 2019. **66**: p. 144-148.
15. Sunnerhagen, K., A. Opheim, and M.A. Murphy, *Onset, time course and prediction of spasticity after stroke or traumatic brain injury.* Annals of physical and rehabilitation medicine, 2019. **62**(6): p. 431-434.