

CORRESPONDENCE FROM REHABILITATION MEDICINE SOCIETY OF AUSTRALIA AND NEW ZEALAND (RMSANZ) LIMITED REGARDING THE PBS LISTINGS OF BOTULINUM TOXIN A

(Agenda item 12.03)

1 Background

- 1.1 Botulinum toxin type A (BoNT-A) is used for the treatment of muscle overactivity and spasticity in patients with cerebral palsy or following a stroke. In correspondence to the PBAC, the Rehabilitation Society of Australia and New Zealand (RMSANZ) claimed that Australia has very restricted BoNT-A access which poses additional quality of life burdens on a marginalised and disadvantaged group, and does not align with clinical best practice.
- 1.2 The correspondence requested that the following changes be made to the PBS listings of BoNT-A to improve equity of access for patients:
- (1) Removal of the requirement that adult cerebral palsy (CP) patients must have commenced treatment with BoNT-A as a paediatric patient;
 - (2) Removal of the limitation of four treatment periods (total BoNT-A) per upper limb per lifetime in post-stroke patients;
 - (3) Reduce the time limitation for first injection of post-stroke upper limb spasticity to less than three months;
 - (4) Removal of the limitation of the non-funding for the post-stroke lower limb; and
 - (5) Expansion of the funded conditions to include muscle overactivity of any aetiology.
- 1.3 The RMSANZ acknowledged that BoNT-A is an expensive medication, but noted that the dosage per injection when used for spasticity was limited and the population requiring its use was small.
- 1.4 Three brands of BoNT-A were listed on the PBS for the indications in Table 1 at the time of PBAC consideration of the correspondence: Botox® (sponsored by Allergan Australia Pty Limited), Dysport® (sponsored by Ipsen Pty Ltd) and Xeomin® (sponsored by Merz Australia Pty Ltd).

Table 1: PBS listed indications for botulinum toxin A, by brand

Indication	PBS listed brands
Urinary incontinence	Botox
Blepharospasm	Botox, Dysport, Xeomin
Hemifacial spasm	Botox, Dysport
Dynamic equinus foot deformity (for patients with cerebral palsy)	Botox, Dysport
Moderate to severe spasticity of the upper limb (for patients with cerebral palsy)	Botox
Moderate to severe spasticity of the upper limb following a stroke	Botox, Dysport, Xeomin
Chronic migraine	Botox
Severe primary axillary hyperhidrosis	Botox
Spasmodic torticollis	Botox, Dysport, Xeomin

Source: Schedule of Pharmaceutical Benefits, 1 July 2018

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- 1.5 In response to a request from the PBAC Executive Committee, the Department requested that the sponsors of BoNT-A advise if recent evidence might support a review of the current restrictions and consider making a formal submission for an expanded listing for BoNT-A. In response to this request, Allergan (the sponsor of Botox®) provided data in support of the RMSANZ requests, including information on the possible financial implications of the requested changes.
- 1.6 A summary of Allergan's response is replicated in Table 2. The claims in Allergan's response have not been evaluated.

Table 2: Summary of Allergan’s response

RMSANZ Request	Allergan response	New Clinical Evidence and Rationale	Financial Implications
<p>1 The requirement that adult CP patients must have commenced treatment with BoNT-A as a paediatric patient</p>	<p>Allergan has not conducted clinical trials in this patient group.</p>	<p>BOTOX is effective and safe in the treatment of spasticity due to cerebral palsy, regardless of patient age.</p> <p>This is supported by current clinical evidence.</p>	<p>Minimal impact because most patients are treated in childhood in Australian clinical practice.</p>
<p>2 The limitation of 4 treatment periods (total BoNT-A) per upper limb per lifetime in post-stroke patients</p>	<p>Allergan has not conducted clinical trials in this patient group.</p>	<p>Some longer term clinical data now exist which demonstrate benefit of further treatment.</p>	<p>Modest impact, based on current utilisation patterns which show that few patients receive 4 treatments.</p>
<p>3 The time limitation for first injection of post-stroke upper limb spasticity</p>	<p>Allergan has not conducted clinical trials in this patient group.</p>	<p>The published literature supports early intervention with BOTOX to maximise patient outcomes.</p>	<p>No impact because the clinical criteria for severity (MAS 3) would be unchanged.</p>
<p>4 Non-funding for post-stroke lower limb treatment</p>	<p>Allergan have conducted trials in this patient group and will submit a major PBAC application for the July 2018 cut-off.</p> <p>Allergan has previously submitted three major applications for BOTOX treatment of this patient group. The last submission was evaluated in 2008. The forthcoming resubmission contains new clinical evidence.</p>	<p>New clinical evidence supports this PBS listing.</p>	<p>New PBS listing. Most of the proposed PBS patients have both upper and lower limb spasticity.</p> <p>The likely change is an increase in number of patients and scripts per lifetime for existing patients (additional doses required for treatment of different muscle groups supporting different functional outcomes).</p>
<p>5 Possible expansion of the funded conditions to include muscle overactivity of any aetiology</p>	<p>Allergan has not conducted clinical trials in this patient group.</p>	<p>Clinical evidence in the form of 6 small RCTs and 12 non-randomised studies supports this expansion.</p> <p>The data confirms improvement in spasticity in these patients who have suffered TBI and SCI that is consistent with their post-stroke counterparts in terms of change in MAS score.</p>	<p>Limited impact because the incidence of TBI and SCI are relatively low compared with the incidence of stroke.</p> <p>The utilisation assumptions for the new restrictions are modelled on those of the post-stroke population (all of them have acute onset).</p>

Source: Allergan response to the request for further information, p1-2.

BoNT-A = botulinum toxin type A; CP = cerebral palsy; MAS = modified Ashworth score; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; RCT = randomised controlled trial; SCI = spinal cord injury; TBI = traumatic brain injury

- 1.7 At the same meeting, the PBAC considered a DUSC review (agenda item 10.6) of the utilisation of BoNT-A supplied through the PBS for the treatment of spasticity in patients with CP or following a stroke, and for spasmodic torticollis, blepharospasm and hemifacial spasm.
- 1.8 In 2017, 13,116 patients were treated with PBS subsidised BoNT-A for spasticity or dystonia. The number of patients receiving treatment has increased steadily with an approximate doubling of the number of patients receiving treatment over the past decade. DUSC considered that this growth rate seemed reasonable noting that there have been a number of extensions to PBS listings over this time and an increase in the number of prescribers of BoNT-A.
- 1.9 The number of patients with CP receiving BoNT-A for upper limb spasticity or foot deformity due to spasticity increased until 2015 and has now stabilised. In 2017, 742 patients were treated with PBS subsidised BoNT-A for upper limb spasticity following a stroke and 1,002 prescriptions were dispensed for this indication. Utilisation of BoNT-A post-stroke is low in the context of all patients who have experienced a stroke and may have resultant spasticity.
- 1.10 DUSC noted that a large proportion of patients (approximately 20% to 45% depending on indication) only had one prescription supplied. This suggests that many patients who initiate BoNT-A may not achieve functional improvement or dislike the injections and cease treatment.
- 1.11 DUSC considered that the cost implications of the first three RMSANZ requests would be small or negligible, but considered that requests 4 and 5 would require major PBAC submissions.

2 PBAC Outcome

- 2.1 The PBAC noted the correspondence from the RMSANZ regarding the PBS listings of BoNT-A and the response from Allergan.
- 2.2 The PBAC recommended the removal of the requirement that adult CP patients must have commenced treatment with BoNT-A as a paediatric patient, as per RMSANZ request (1). The PBAC noted the advice from RMSANZ that there is no observable differentiation in response for adult CP patients based on whether or not they received BoNT-A as a child. The PBAC considered that the financial implications of this change would be negligible, based on information provided by RMSANZ, DUSC and Allergan.
- 2.3 The PBAC thanked Allergan for its response. The PBAC noted Allergan had submitted a major submission for consideration at the November 2018 PBAC meeting requesting PBS listing for adult lower limb focal spasticity, in line with RMSANZ's request (4).
- 2.4 The PBAC noted Ipsen (the sponsor of Dysport®) had submitted two major submissions for consideration at the November 2018 PBAC meeting. One was to extend the listing of BoNT-A for moderate to severe spasticity of the upper limb from following a stroke to following an acute event (such as stroke, traumatic brain

injury, infection or hypoxia) that leads to an upper motor neuron lesion resulting in spasticity (i.e. RMSANZ request 5) and to remove the current four-treatment period per lifetime restriction (i.e. RMSANZ request 2). The second submission was for a new listing of BoNT-A for the treatment of lower limb spasticity in patients following an acute event (i.e. RMSANZ request 4 and 5).

- 2.5 The PBAC deferred consideration of RMSANZ’s remaining request (3). The PBAC noted its intent to discuss this request in conjunction with the major submissions from Allergan and Ipsen at its November 2018 meeting.

3 Recommended listing

- 3.1 Amend existing listings as follows:

Name, Restriction, Manner of administration and form	Max qty packs	Max qty units	No. of repeats	Proprietary Name and Manufacturer
BOTULINUM TOXIN TYPE A Botulinum toxin type A 100 units injection, 1 vial	4	4	0	Botox® Allergan

Category / Program:	Section 100 – Botulinum Toxin Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS indication:	Dynamic equinus foot deformity (5407)
Restriction level / Method:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria:	The condition must be due to spasticity, AND Patient must have cerebral palsy, AND Patient must be ambulant, AND Patient must have commenced PBS-subsidised treatment with Botulinum Toxin Type A Neurotoxin Complex as a paediatric patient.
Population criteria:	Patient must be aged 18 years or older.
Treatment criteria:	Must be treated by a neurologist; OR Must be treated by an orthopaedic surgeon; OR Must be treated by a paediatrician; OR Must be treated by a rehabilitation specialist.

Category / Program:	Section 100 – Botulinum Toxin Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS indication:	Moderate to severe spasticity of the upper limb (5261)
Restriction level / Method:	<input checked="" type="checkbox"/> Streamlined

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Clinical criteria:	Patient must have cerebral palsy, AND Patient must have commenced PBS subsidised treatment with Botulinum Toxin Type A Neurotoxin Complex as a paediatric patient.
Population criteria:	Patient must be aged 18 years or older.
Treatment criteria:	Must be treated by a neurologist; OR Must be treated by an orthopaedic surgeon; OR Must be treated by a paediatrician; OR Must be treated by a rehabilitation specialist; OR Must be treated by a plastic surgeon.
Note:	Contact the Department of Human Services before commencing PBS subsidised treatment in cerebral palsy patients who have been treated for moderate to severe spasticity of the upper limb with non-PBS subsidised botulinum toxin prior to the age of 18.

Name, Restriction, Manner of administration and form	Max qty packs	Max qty units	No. of repeats	Proprietary Name and Manufacturer
CLOSTRIDIUM BOTULINUM TYPE A TOXIN- HAEMAGGLUTININ COMPLEX Clostridium botulinum type A toxin-haemagglutinin complex 500 units injection, 1 vial	2	2	0	Dysport® Ipsen

Category / Program:	Section 100 – Botulinum Toxin Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS indication:	Dynamic equinus foot deformity (5332)
Restriction level / Method:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria:	The condition must be due to spasticity, AND Patient must be an ambulant cerebral palsy patient, AND Patient must have commenced PBS subsidised treatment with clostridium botulinum type A toxin haemagglutinin complex as a paediatric patient.
Population criteria:	Patient must be aged 18 years or older.
Treatment criteria:	Must be treated by a neurologist; OR Must be treated by an orthopaedic surgeon; OR Must be treated by a paediatrician; OR Must be treated by a rehabilitation specialist.

Name, Restriction, Manner of administration and form	Max qty packs	Max qty units	No. of repeats	Proprietary Name and Manufacturer
CLOSTRIDIUM BOTULINUM TYPE A TOXIN-HAEMAGGLUTININ COMPLEX Clostridium botulinum type A toxin-haemagglutinin complex 300 units injection, 1 vial	4	4	0	Dysport® Ipsen

Category / Program:	Section 100 – Botulinum Toxin Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS indication:	Dynamic equinus foot deformity (5332)
Restriction level / Method:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria:	The condition must be due to spasticity, AND Patient must be an ambulant cerebral palsy patient, AND Patient must have commenced PBS-subsidised treatment with clostridium botulinum type A toxin haemagglutinin complex as a paediatric patient.
Population criteria:	Patient must be aged 18 years or older.
Treatment criteria:	Must be treated by a neurologist; OR Must be treated by an orthopaedic surgeon; OR Must be treated by a paediatrician; OR Must be treated by a rehabilitation specialist.

4 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.