PUBLIC SUMMARY DOCUMENT
Product: Botulinum toxin type a purified neurotoxin complex, Lyophilised powder for I.M. injection 100 units vial, Botox®
Sponsor: Allergan Australia Pty Ltd
Date of PBAC Consideration: July 2008

1. Purpose of Application

The re-submission sought to extend the Section 100 listing (under the Botulinum Toxin Program) for botulinum toxin type A (BTx-A) to include the treatment of moderate to severe spasticity of the upper limb in adults following a stroke as an adjunct to physical therapy.

2. Background

At the November 2005 PBAC meeting, the PBAC rejected an application to extend the Section 100 listing for botulinum toxin type A (Botox) to include the treatment of focal spasticity in adults because of uncertainty with interpreting the extent of clinically relevant benefits arising from the spasticity outcomes analysed by the trials, uncertainty associated with the modelled physiotherapy cost off-sets and the resulting unacceptable and uncertain cost-effectiveness. *(See also PBAC Public Summary Document November 2005)*

At the July 2006 PBAC meeting, the PBAC again rejected a submission seeking for the treatment of focal spasticity (upper and lower limbs) in adult patients who meet certain criteria because of uncertainty in extrapolation of response in terms of the Ashworth scale to a quality of life measure, and high and uncertain cost-effectiveness. *(See also PBAC Public Summary Document July 2006)*

3. Registration Status

Botulinum Toxin Type A Purified Neurotoxin Complex is indicated for:

- Treatment of blepharospasm associated with dystonia, including benign blepharospasm and VII nerve disorders (specifically hemifacial spasm) in patients twelve years and over;
- Treatment of cervical dystonia (spasmodic torticollis);
- Treatment of dynamic equinus foot deformity due to spasticity in juvenile cerebral palsy patients two years of age or older;
- Treatment of severe primary hyperhidrosis of the axillae;
- Treatment of glabellar lines associated with corrugator and/or procerus muscle activity;
- Treatment of focal spasticity in adults;
- Treatment of spasmodic dysphonia;
- Treatment of strabismus in children and adults.

4. Listing Requested and PBAC's View

The re-submission requested listing consistent with Clostridium botulinum type A toxin (Dysport®) for upper limb spasticity.

Section 100 Botulinum Toxin Program

Note:
Arrangements to prescribe this item should be made by medical practitioners with Medicare Australia, 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.

Treatment of moderate to severe spasticity [defined as MAS greater than or equal to 3 using modified Ashworth scale] of the upper limb in adults following a stroke, as second line therapy when standard management has failed (e.g. physiotherapy and/or oral spasticity agents) or as an adjunct to physical therapy.
Maximum number of treatments to be authorised is 4 per upper limb per lifetime. Treatment should not be initiated until 3 to 6 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.
Contraindications to treatment include established severe contracture, known sensitivity to botulinum toxin.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Botox injection therapy treats spasticity by allowing the muscle to relax. The effects of Botox are reversible and treatment provides a window of opportunity in which other treatments such as physiotherapy can be used to regain muscle or joint function.

6. Comparator

The submission nominated clostridium botulinum (Dysport®) as the main comparator. The PBAC considered this was appropriate.

7. Clinical Trials

The re-submission presented an indirect meta-analysis of five direct randomised trials of BTx-A and six Dysport® trials in upper limb with placebo as common comparator. The meta-analysis was based on mean change in Ashworth score in wrist, elbow and finger flexor muscles, although the Dysport® studies used Modified Ashworth scale to measure spasticity.

The key trials and associated reports published at the time of the re-submission are as follows:

Trial ID/First Author	Protocol title / Publication title	Publication citation
BTx-A vs placebo		
008 Brashear A., et al,2002	Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke.	New England Journal of Medicine 347:395–400, 2002.
130 Simpson D.M., et al Simpson 1996	Double-blind, vehicle-controlled study to evaluate dosing, safety and efficacy of intramuscular botulinum toxin type A in upper limb spasticity post-stroke.	Neurology 46:1306–10, 1996.
133/134 Childers M.K., et al 2004	Multicenter, double-blind, placebo-controlled, parallel, dose-response clinical trial of intramuscular BTx-A in upper limb spasticity post-stroke	Archives of Physical Medicine and Rehabilitation 85:1063–9, 2004.
418/422 De Beyl Z, et al	Multicenter, double-blind, vehicle - controlled, parallel study to evaluate dosing, safety and efficacy of intramuscular	European Journal of Neurology 7(Suppl 3):23, 2000.

2000	BTx-A in upper limb spasticity post-stroke	
Dysport® vs placebo		
Bakheit A.M., et al 2000	A randomized, double-blind, placebo-controlled, dose-ranging study to compare the efficacy and safety of three doses of botulinum toxin type A (Dysport®) with placebo in upper limb spasticity after stroke.	Stroke, 31:2402–6, 2000.
Bakheit A.M., et al 2001	A randomized, double-blind, placebo-controlled study of the efficacy and safety of botulinum toxin type A in upper limb spasticity in patients with stroke.	European Journal of Neurology,1;8:559–65, 2001.
Bhakta B.B.,et al 2000	Randomized double-blind placebo-controlled trial of botulinum toxin treatment on the disabling effects of severe arm spasticity in stroke.	Clinical Rehabilitation,14:213, 2000.
Hesse S., et al 1998	Botulinum toxin type A and short-term electrical stimulation in the treatment of upper limb flexor spasticity after stroke: a randomized, double-blind, placebo-controlled trial.	Clinical Rehabilitation. 12:381–8, 1998.
Smith S.J., et al 2000	A Botulinum toxin type A and short-term electrical stimulation in the treatment of upper limb flexor spasticity.	Clinical Rehabilitation, 14:5–13, 2000.
Suputtitada A., et al 2005	The lowest effective dose of botulinum A toxin in adult patients with upper limb spasticity.	Disability and Rehabilitation, 27(4):176–184, 2005.

8. Results of Trials

The key results of the meta-analyses of BTx-A or Dysport® vs. placebo trials are summarised in the table below.

Outcome (Mean change in Ashworth score)	**Assessment**	**BTx-A vs. placebo**		**Dysport® vs. placebo**	
		Result	**P value**	**Result**	**P value**
Wrist flexor tone	WMD (95%CI)	–0.74 (–1.05,–0.42)	<0.0001	-0.80 (-1.37, -0.23)	<0.05
Elbow flexor tone	WMD (95%CI)	–0.30 (–0.52,–0.10)	0.004	-0.49 (-0.69, -0.28)	<0.05
Finger flexor tone	WMD (95%CI)	–0.26 (–0.75,0.22)	0.29	–1.34 (-2.35,-0.33)	<0.05
Responder *	RD (95%CI)	0.36 (0.25,0.46)	<0.001	0.32 (0.15,0.49)	<0.001

* patient with a reduction in tone of ≥2 in Ashworth score in any muscle
WMD weighted mean difference; RD risk difference; CI confidence interval

The data indicated that both botulinum toxin type A and clostridium botulinum treatment resulted in a statistically significant difference in mean change in Ashworth score (Modified Ashworth Score for clostridium botulinum) in wrist and elbow flexor muscles and responder rate compared to placebo.

For PBAC's comments on these results, see Recommendation and Reasons.

The re-submission also presented the following new toxicity data:

a) comparison of discontinuations rates in the meta-analysis of five randomised control trials (RCTs) of BTx-A and six RCTs of Dysport®; and

b) data from post marketing surveillance.

The rate of discontinuations were similar across the BTx-A vs placebo and Dysport vs placebo. However, there are recent concerns regarding the safety profile of BTx-A from various drug regulatory agencies: FDA, Health Canada and Medicines and Healthcare Products Regulatory Agency (MHRA) due to distant spread of BTx-A from the site of injection.

9. Clinical Claim

The submission claimed that BTx-A was no worse in terms of effectiveness and had similar toxicity to Dysport®. The PBAC accepted this claim.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The re-submission presented a cost minimisation analysis. The equi-effective doses were estimated as BTx-A 229U per treatment course and Dysport® 989U per treatment course.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The re-submission estimated that the likely number of patients/year to be less than 10,000 in Year 2 equating to a financial cost/year to the PBS of between $10 – 30 million in Year 2. These costs were based on a dose of 229U, the average dose across the key trials.

12. Recommendation and Reasons

The PBAC recommended an extension to the Section 100 listing for Botulinum toxin type A to include the treatment of moderate to severe spasticity of the upper limb in adults following a stroke, as second line therapy when standard management has failed or as an adjunct to physical therapy, on a cost-minimisation basis compared with clostridium botulinum. The equi-effective doses are botulinium toxin type A 229U per treatment course and clostridium botulinum 989U based on the trial data. The PBAC noted that Botulinum toxin type A Botox® would be required to join the current Risk Sharing Arrangement that is in place for the Dysport®, and that this agreement should include limits that do not allow patients to have four treatments each per formulation.

The PBAC noted there is some uncertainty regarding the methods used in the submission as there was no formal indirect comparison between the meta-analysis results presented for the two agents. Notwithstanding this, the data indicated that both botulinum toxin type A and clostridium botulinum treatment resulted in a statistically significant difference in mean change in Ashworth score (Modified Ashworth Score for clostridium botulinum) in wrist and elbow flexor muscles and responder rate compared to placebo. The PBAC considered that the two products, although not bioequivalent, can be expected to have similar clinical outcomes. This is seen particularly in the responder rate (response was defined as an Ashworth score change of greater than or equal to two) notwithstanding the limited number of trials.

The PBAC considered the restriction should be the same as for the currently listed clostridium botulinum for post-stroke upper limb spacticity, however that the maximum total number of botulinum treatments authorised be limited to 4 per upper limb, per lifetime. The PBAC considered that the cost effectiveness would be unacceptable if the number of treatments increased to 4 per each formulation.

Recommendation
Add the following to the restriction under the BOTULINUM TOXIN PROGRAM

To be finalised.

Section 100 (Botulinum Toxin Program)

Botulinum toxin type A purified neurotoxin complex
Treatment of moderate to severe spasticity [defined as MAS greater than or equal to 3 using modified Ashworth scale] of the upper limb in adults following a stroke, as second line therapy when standard management has failed (e.g. physiotherapy and/or oral spasticity agents) or as an adjunct to physical therapy.
Maximum number of treatments to be authorised is 4 (total Botox and Dysport) per upper limb per lifetime. Treatment should not be initiated until 3 to 6 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.
Contraindications to treatment include established severe contracture, known sensitivity to botulinum toxin.

Note:
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Note:
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Pack size: 1

13. 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.

14. Sponsor's Comment

The sponsor believes botulinum toxin provides a valuable long-term treatment option for patients following a stroke. The sponsor acknowledges and supports the decision by the PBAC and it will examine ways to demonstrate the longer-term benefits of treatment to the committee.