

Cost Effectiveness of Long-Term Incobotulinumtoxin-A Treatment in the Management of Post-stroke Spasticity of the Upper Limb from the Australian Payer Perspective

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Abstract

Background In Australia, the reimbursement of botulinum neurotoxin-A (BoNT-A) on the Pharmaceutical Benefits Scheme for the treatment of moderate to severe spasticity of the upper limb following a stroke (PSS-UL) is restricted to four treatment cycles per upper limb per lifetime. This analysis examined the cost effectiveness of extending the treatment beyond four treatments among patients with an adequate response to previous treatment cycles.

Methods A Markov state transition model was developed to perform a cost-utility analysis of extending the use of incobotulinumtoxin-A beyond the current restriction of four treatment cycles among patients who have shown a successful response in previous treatment cycles ('known responders'). The Markov model followed patients in 12-weekly cycles for 5 years, estimating the proportion of patients with or without response over this period in each of the modelled treatment arms. Post hoc analysis of an open-label extension phase study informed the Markov model. The perspective of the analysis was the Australian healthcare system, meaning only direct healthcare costs were included. Utility values by response status were derived from EQ-5D data from a published double-blind, placebo-controlled study. The primary outcome measure was the incremental cost per quality-adjusted life-year (QALY). Univariate and probabilistic sensitivity analyses were conducted.

Results The open-label extension study data demonstrated the probability of treatment response after four injections was greater among 'known responders' than those without prior response. The incremental cost per QALY gained of continued use of incobotulinumtoxin-A beyond the current restriction of four treatments was A\$59,911.

Conclusion Limiting BoNT-A treatment to four cycles per patient per lifetime is likely to be suboptimal in many patients with PSS-UL. Treatment response beyond four cycles is highest among known responders, and allowing such patients to continue treatment beyond four cycles appears cost effective.

Key Points for Decision Makers

In Australia, reimbursement of BoNT treatment is restricted to a maximum of four treatment cycles per upper limb per lifetime, irrespective of clinical need or efficacy of prior response.

A cost-effectiveness analysis of extending the treatment beyond four treatments among patients with an adequate response to previous treatment cycles has not been performed from the perspective of the Australian healthcare system.

This analysis found that continuing incobotulinumtoxin-A treatment in patients with moderate to severe PSS-UL beyond four cycles can be cost effective. For this to be realised, careful patient selection is required so that treatment is targeted towards those with the greatest likelihood of continuing to respond to multiple treatment cycles.

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1 Introduction

Spasticity is a movement disorder associated with pathologically increased muscle tone, often a complication from stroke. It has been defined as “a motor disorder characterised by a velocity-dependent increase in tonic stretch reflexes with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex” [1]. Muscle tone is defined as a continuous steady-state contraction of the muscles, which, under normal circumstances, enables a normal posture through a balance of extensor and the flexor muscle tone. Post-stroke spasticity of the upper limb (PSS-UL) adversely affects this balance and imposes considerable burden on the patient, creating stiffness and resistance to movement. Many patients experience a negative impact on their ability to perform activities of daily living such as personal hygiene and dressing, necessitating the help of a family member or professional caregiver [2]. Spasticity can also cause significant pain and discomfort.

Spasticity in the upper limb affects between 19 and 38% of stroke survivors during the first year after stroke [3–5]. In Australia, the incidence of stroke is 0.14% each year [6], which equates to approximately 35,000 stroke cases, suggesting that more than 13,000 persons may experience post-stroke spasticity (PSS) in Australia each year. The extent of disability and compromised functional ability strongly influences post-stroke dependency and care requirements.

The use of botulinum neurotoxin-A (BoNT-A) for PSS-UL is well-established in Australian clinical practice. The European consensus statement recommends BoNT-A by acknowledging its effectiveness and safety supported by clinical evidence from 20 randomised controlled trials (RCTs) and two meta-analyses [7]. Similar findings and recommendations have also been put forward by the American Academy of Neurology [8]. It has been suggested that the most reasonable approach is to treat PSS whenever it becomes problematic or disabling [9]. The Clinical Guidelines for Stroke Management released by the National Stroke Foundation of Australia in 2010 recommend stroke survivors with persistent moderate to severe spasticity that interferes with activity or personal care be treated with BoNT-A [10]. The use of BoNT-A should be seen as part of an integrated programme of care and thus it should be provided along with other care such as physiotherapy rather than being administered in isolation.

Incobotulinumtoxin-A (NT 201/Xeomin[®]; Merz Pharmaceuticals GmbH, Frankfurt, Germany) is a highly purified BoNT-A formulation. A phase III, placebo-controlled, randomised study of incobotulinumtoxin-A demonstrated a statistically significant reduction in muscle tone and improvement in functionality following a single treatment

cycle in 148 patients with PSS-UL compared with placebo [11]. Nearly 70% of patients treated with incobotulinumtoxin-A successfully responded to the treatment, with a ≥ 1 -point improvement in the Ashworth Scale score at a control visit 4 weeks post injection. This trial was followed by an open-label extension study that demonstrated sustained improvements in muscle tone and functionality over a study duration of up to 89 weeks. The treatment was well-tolerated during repeated treatment cycles [12]. The results from a recent randomised, double-blind, placebo-controlled study by Elovic et al. [13] that included 259 patients followed-up for up to 48 weeks in the full analysis set for the efficacy analysis, corroborated the results from Kaňovský et al. [11].

In Australia, BoNT-A is reimbursed through the Pharmaceutical Benefits Scheme (PBS) for multiple indications, including the treatment of moderate to severe PSS-UL. Three BoNT-A preparations are available on the PBS: incobotulinumtoxin-A (Xeomin[®]); onabotulinumtoxin-A (Botox[®]) and abobotulinumtoxin-A (Dysport[®]). The use of BoNT-A on the PBS is subject to strict eligibility criteria. Treatment is restricted to adult patients free of established severe contracture in the treated limb and who had a stroke more than 2 months prior. Patients with spasticity due to brain trauma other than stroke are ineligible for treatment. The treatment must be second-line after not responding to standard management, and be provided adjunctively with physiotherapy. Reimbursed treatment is ceased if the patient fails to respond, defined as a failure to decrease spasticity by 1, using the Modified Ashworth Scale (MAS), in at least one joint after two treatment cycles.

Importantly, treatment is limited to a maximum of four treatment cycles per upper limb per lifetime, irrespective of the patient's clinical need or the efficacy of prior response. Imposing a limit to the maximum BoNT-A treatment cycles is not entirely consistent with evidence-based guidelines [7]. Furthermore, this limitation is unique to Australia when compared with all other jurisdictions where BoNT-A injections are funded for the treatment of PSS-UL. For example, the Scottish Medicines Consortium (SMC) accepted the use of BoNT-A for patients with PSS-UL, without restrictions on the number of injections permitted over a patient's lifetime (Botox[®], SMC 2011 [14]; Xeomin[®], SMC 2011 [15]). It is possible the PBS restriction will result in suboptimal treatment outcomes in some patients in the long-term. This is especially likely among patients who have shown a successful response and who require ongoing re-injections for maintenance of response.

This analysis presents a modelled cost-utility analysis (CUA) that estimates the cost and health implications of extending incobotulinumtoxin-A treatment beyond four treatment cycles in patients who are ‘known responders’.

2 Methods

2.1 Model Structure

A Markov state transition model was developed to perform the CUA. This approach was the preferred modelling methodology due to its simplicity and transparency (when compared with other modelling techniques such as microsimulation). The model structure compared a scenario where ‘known responders’ continued treatment past four injections while maintaining a positive treatment response with the current scenario where they are forced to stop BoNT-A after four cycles, i.e. current standard of care (SoC). Patients failing to achieve or maintain response are discontinued from treatment. This model structure is illustrated in Fig. 1.

A successful response was defined as a ≥ 1 -point improvement in the MAS, a well-known and commonly used scale in clinical trials with spasticity [3, 16, 17]. The MAS is a simple 5-point scale that enables clinicians to quantify the amount of muscle resistance encountered during passive movements, and is considered to be the best clinical tool for measuring resistance to movement [18].

Scores range from 0 to 4, with lower scores indicating less resistance to passive movement (i.e. better muscle tone).

The Markov model consisted of health states defined by response to BoNT-A treatment or SoC alone, with a hypothetical cohort of patients transiting between these health states in 12-weekly cycles over the 5-year model duration. The 12-week model cycle was selected to reflect a typical interval between BoNT-A doses according to recommendations in the Australian Product Information for incobotulinumtoxin-A, and patients in Australia are unlikely to receive more frequent re-injection cycles in practice. Figure 1 illustrates the transition of patients through the Markov model. All patients began in the model by receiving the first injection. A proportion of these patients transited to the ‘incobotulinumtoxin-A + SoC and in response’ health state by achieving an Ashworth Scale of ≥ 1 -point gain from baseline, while others transited to the ‘incobotulinumtoxin-A + SoC and not in response’ health state if they failed to achieve this level of response. All patients received a re-injection in the second model cycle; however, patients who failed to respond to both the first and second treatments transited to the ‘SoC alone and not in response’ health state. After the fourth injection, all ‘in

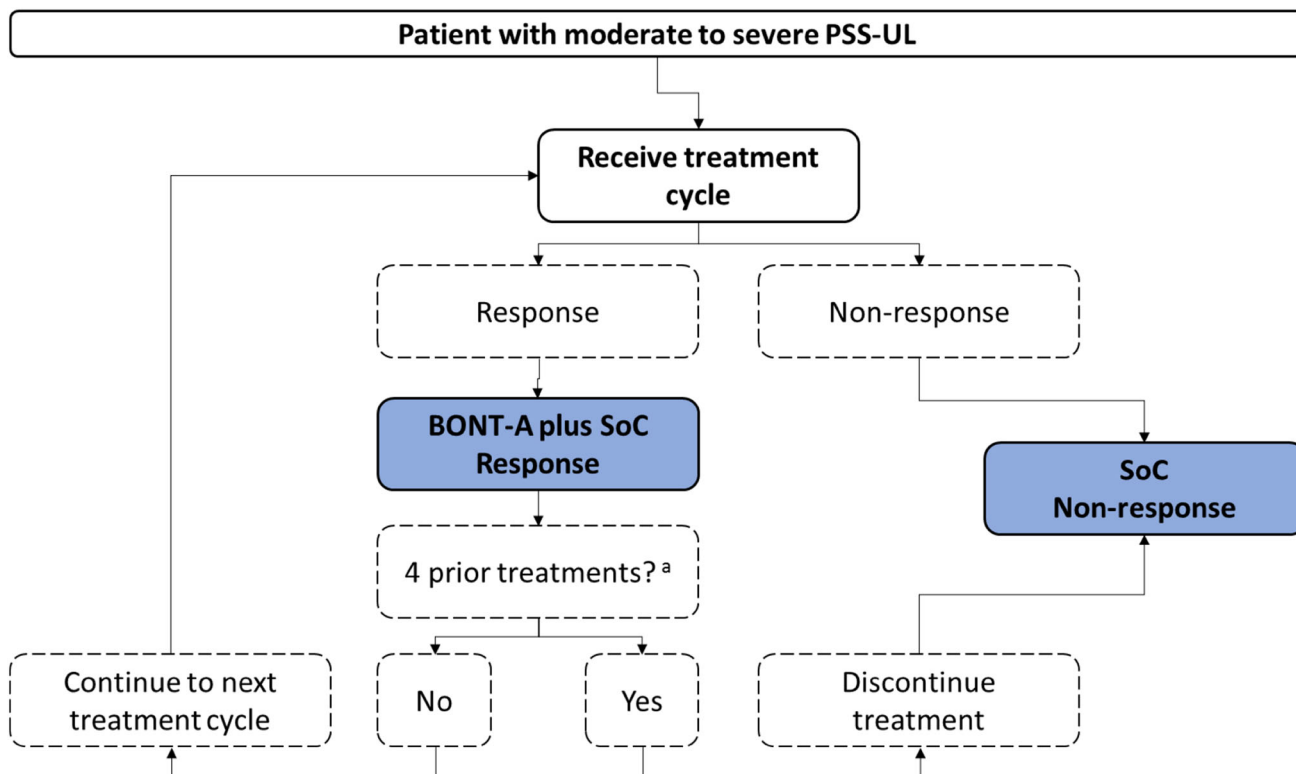


Fig. 1 Model structure showing Markov health states in the management of PSS-UL. Shaded boxes represent the Markov health states in which patients reside from one Markov cycle to the next. Dashed outline boxes represent the possible transitions between health states at each Markov cycle. ^a The dichotomy of the four prior

treatments is only applied in the comparator arm of the model. In the treatment arm of the model, all patients are allowed to continue to the next treatment cycle if they maintain a response. SoC standard of care, BONT-A botulinum neurotoxin-A, PSS-UL post-stroke spasticity of the upper limb

response' patients in the current PBS regimen arm were transferred to the SoC-alone strategy. In the base-case model, these patients were assumed to lose response after stopping treatment. In contrast, patients in the treatment arm continued as long as they maintained the response in each successive treatment cycle. Patients faced a risk of death at each modelling cycle, as informed by Australian life tables.

The primary outcome measure of the model was the number of quality-adjusted life-years (QALYs); the incremental cost-effectiveness ratio (ICER) was expressed in terms of incremental cost per QALY gained. The base-case model horizon was set at 5 years. A 5-year horizon was considered to be sufficiently long enough to assess the long-term cost effectiveness of treatment without introducing unnecessary extrapolation-related uncertainties. The perspective of the analysis was the Australian health-care system, meaning only direct healthcare costs were included. All cost and health outcomes are discounted at 5%, as currently required by the Pharmaceutical Benefits Advisory Committee (PBAC) submission guidelines. Costs are expressed in Australian dollars (2016 values).

A series of univariate deterministic sensitivity analyses were conducted on the base case by altering data inputs for key model variables. Probabilistic sensitivity analysis (PSA) was also conducted on the base case, with distributions assigned to the response rate and the utility scores. Uncertainties associated with these variables were described by the beta distribution.

All clinical inputs for this model were sourced from a placebo-controlled, randomised trial [11] and its extension study [12], providing the model with a strong faithfulness to the available trial data. While extrapolation was necessary for an adequate assessment of cost effectiveness, the model should hence have interval validity. The patient population represented in the trial was also reasonably generalisable to Australian patients who were eligible for BoNT-A treatment on the PBS, ensuring the external validity of model outputs.

2.2 Model Variables

Efficacy data for incobotulinumtoxin-A were provided by a placebo-controlled, randomised trial [11], which was the pivotal study used to inform the incobotulinumtoxin-A PBAC submission in 2014, and its extension study [12], as summarised in Table 1. A post hoc analysis of the extension-phase data was conducted to derive response rates in the long-term. The initial response rate was informed by the placebo-controlled trial, where 68.5% of patients successfully responded to incobotulinumtoxin-A by achieving a ≥ 1 -point improvement in Ashworth Scale score at a control visit 4 weeks post injection. The post hoc analysis

of the extension phase data indicated a response rate of 70.0% for these patients in the second treatment cycle. The response rate in subsequent treatment cycles for known responders was 87.2%.

Patient demographics of the modelled cohort were also based on an open-label extension study [12]. The only characteristics relevant to the model were age and sex, both of which affect the risk of death at each cycle in the model. The baseline age was 57 years, with 64% being male.

All cost inputs are presented in Table 1. Only cost items that were directly related to the administration of incobotulinumtoxin-A were considered, including costs of drug acquisition and injection procedures. All costs were in Australian dollars (2016 values).

The drug acquisition cost per treatment was determined on the number of 100-unit (U) vials required per treatment. The number of vials required was informed by mean doses of incobotulinumtoxin-A in the extension study. The mean dose per treatment was 352 U, thus requiring 3.52 100-U vials per treatment. This dose was consistent with the recommended dose in the Australian Product Information. The cost per 100-U vial was A\$375.00, as per the current PBS price. A pharmacy mark-up and dispensing fee (\$47.02) are also added on to the total drug acquisition cost.

The cost of treatment administration was based on the Australian Medicare Benefits Schedule (MBS). Each administration procedure was assumed to be associated with a specialist consultation (MBS item number 116; \$75.50) and other services associated with the administration procedure (e.g. injection, neuromuscular stimulation, ultrasound). To determine the extent of these services per injection, an analysis of a 10% sample of MBS claims data between 2010 and 2014 was performed [19]. On average, each administration was associated with an estimated cost of \$230.03 attributable to the injection procedure itself and the electrical stimulation and/or ultrasound imaging to guide the identification of injection site(s) (see Table 1). In total, administration costs of \$305.53 (\$75.50 for pre-/post-injection consultation and \$230.03 for the procedure itself) are hence applied at each injection.

Quality of life (QoL) was entirely dependent on treatment response in the current model. Utility values were derived from EQ-5D data from a double-blind, placebo-controlled study [11], with Australian preference weights applied [20]. Patients in the response health state accrued a utility value of 0.51 (standard deviation [SD] 0.32), while those not in response accrued a utility value of 0.39 (SD 0.24), which was the EQ-5D utility value of the population at baseline.

Adverse events and their potential cost implications were not explicitly captured in the model; however, these were considered as relatively minor and transient and

Table 1 Model inputs for the base-case analysis

Model variable	Base-case input	Source
Rate of response to incobotulinumtoxin-A		
First injection (<i>n/N</i> ; SE)	0.6849 (50/73; 0.054)	Placebo-controlled double-blind RCT [11]
Second injection, initial responders (<i>n/N</i> ; SE)	0.7917 (38/48; 0.059)	Post hoc analysis of extension-phase data [12]; response rates for patients who maintained response in successive re-injections
Second injection, initial non-responders (<i>n/N</i> ; SE)	0.7000 (14/20; 0.102)	Data from the third injection include patients crossed over from placebo at the second injection (i.e. start of the extension phase)
Third injection (<i>n/N</i> ; SE)	0.8539 (76/89; 0.037)	
Fourth injection (<i>n/N</i> ; SE)	0.9206 (58/63; 0.034)	
Fifth injection (<i>n/N</i> ; SE)	0.9211 (35/38; 0.044)	
Applied in the model for two or more injections, mean of second to fifth injections (<i>n/N</i> ; SE)	0.8264 (257/311; 0.021)	
Cost inputs		
Price per 100-U vial	A\$375.00	PBS schedule
Number of vials per treatment cycle	3.52	Mean dose during the extension phase [12]. No wastage is assumed
Pharmacy mark-up and dispensing fee per treatment cycle	A\$47.02	PBS section 100 pricing requirements
Administration cost per treatment cycle	A\$305.53	MBS. The average resource use per injection is as follows (based on the 2010–2014 MBS claims data ^a) MBS item 116 for consultation at A\$75.50 × 1 (assumption) MBS item 18365 for injection at A\$124.85 × 1.28 MBS items 11012/11015/11018 for electrical stimulation at A\$112.00 × 0.43/A\$149.90 × 0.02/A\$223.95 × 0.08 MBS item 55804 for ultrasound at A\$109.10 × 0.01
Total cost per treatment cycle	A\$1672.55	Calculated
Utility inputs		
Non-response (SD)	0.39 (0.24)	Post hoc analysis of EQ-5D data from the placebo-controlled, double-blind RCT [11]
In response (SD)	0.51 (0.32)	

PBS Pharmaceutical Benefits Scheme, *MBS* Medicare Benefits Scheme, *n* number of responders, *N* number of subjects treated in the respective cycle, *SD* standard deviation, *SE* standard error, *RCT* randomized controlled trial, *BoNT-A* botulinum neurotoxin-A

^aAll MBS fees are as of April 2017. The current MBS item for BoNT-A injections for the treatment of moderate to severe spasticity of the upper limb (MBS item 18365) did not become available until April 2015. The claims data were only available to 2014. For the purpose of the data analysis, all patient records with claims for the relevant MBS items then available (18360 for onabotulinumtoxin-A, and 18364 for abobotulinumtoxin-A) were extracted (= ‘flag claims’), and other resource uses on the same day of ‘flag claims’ (but only those considered as specifically relevant to the treatment of upper limb spasticity) were counted to inform the estimates above

unlikely to be associated with meaningful cost implications overall.

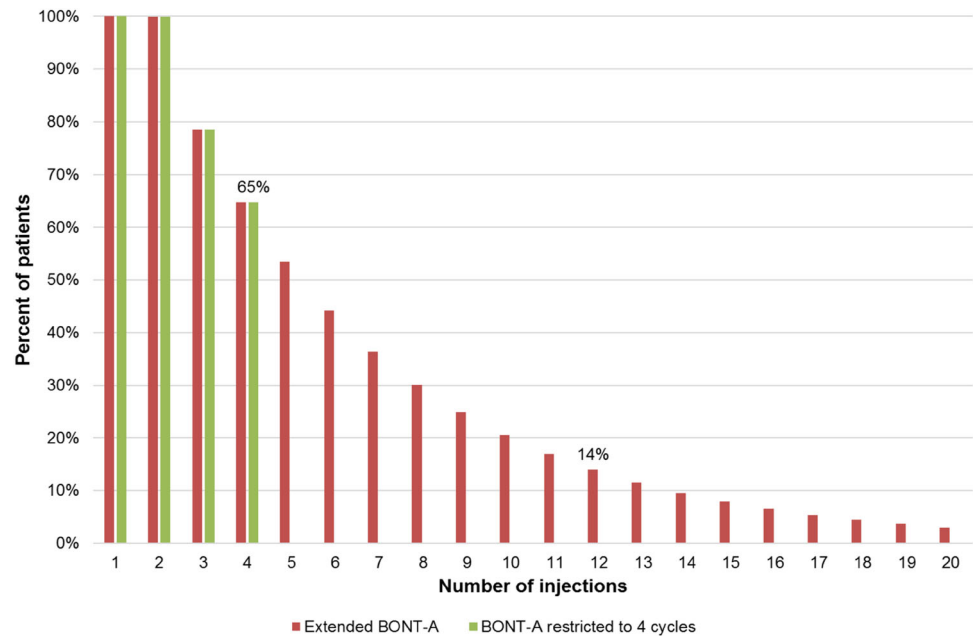
3 Results

Patients in the extended treatment arm of the model received an average of 6.49 injections compared with 3.43 injections in the comparator arm. In the extended treatment arm of the model, 14% of patients received 12 or more

injections (Fig. 2). These additional treatments meant additional costs of \$4533 per patient and provided an additional 0.08 QALYs per patient due to the longer time spent in response when compared with the current PBS restrictions. The incremental cost per QALY gained of extending BoNT-A treatment for PSS-UL beyond the current restriction of four treatment cycles was A\$59,911 (Table 2).

A series of univariate deterministic sensitivity analyses were performed (Table 3). As expected, the incremental

Fig. 2 Proportion of patients remaining on BoNT-A treatment over time: extended BONT-A compared with current PBS restrictions (maximum of four treatment cycles). *BONT-A* botulinum neurotoxin-A, *PBS* Pharmaceutical Benefits Scheme



benefit of a response in terms of utility was the most influential variable. Altering the extent of utility gain associated with response by using the 95% confidence interval produced ICERs ranging from A\$44,933 to A\$89,867. Sensitivity analyses also explored the occurrence of natural disease resolution, which had a minor impact on the ICER (\$59,934 for 5% natural disease resolution per annum and \$59,954 for no natural disease resolution). This minimal impact to the overall cost effectiveness is because the rate of disease resolution affects both treatment arms equally.

A PSA was performed using 1000 iterations of the base-case evaluation. Beta distributions were applied to response rates and utility values to capture the underlying uncertainty based on the base-case mean values and standard errors from the available data (see Table 1). No distributions in cost variables were applied as the base-case values used fixed fees per service.

Across the 1000 iterations, the extended treatment regimen was demonstrated to produce a mean QALY gain of 0.0758 (95% credible interval [CrI] 0.0747–0.0768) at a

mean additional cost of A\$4531 (95% CrI \$4527–\$4535) (see Fig. 3). The cost-effectiveness acceptability curve (Fig. 4) illustrates probabilities the extended treatment regimen would be cost effective at various willingness-to-pay thresholds. At the willingness-to-pay threshold of A\$60,000 per QALY, the probability of the extended treatment regimen being cost effective was 51%.

4 Discussion

This modelled CUA estimated the cost effectiveness of continuing the use of incobotulinumtoxin-A beyond four treatment cycles for the management of PSS-UL. The model is based on a post hoc analysis of previously published extension study data [12]. These analyses suggest that the likelihood of achieving and maintaining alleviation in muscle tone could be improved by selecting patients with response to previous treatment cycles. The current study also highlighted that the QoL of patients living with PSS-UL was considerably compromised, with an estimated

Table 2 Results of the CUA of the extended incobotulinumtoxin-A regimen compared against the current PBS subsidised regimen of incobotulinumtoxin-A (maximum of four treatment cycles)

Model outputs	Extended regimen	Current PBS regimen	Incremental difference
Total costs (A\$)	A\$10,189	A\$5656	A\$4533
QALYs	1.876	1.800	0.076
ICER			A\$59,911

QALYs quality-adjusted life-years, *ICER* incremental cost-effectiveness ratio, *PBS* Pharmaceutical Benefits Schedule, *CUA* cost-utility analysis
All outputs are discounted at 5% per annum

Table 3 Univariate deterministic sensitivity analyses

Model variable/assumptions tested	Incremental cost	Incremental QALY	ICER
Base-case results	A\$4533	0.0757	A\$59,911
Model duration, years			
1	A\$855	0.0201	A\$42,581
2	A\$2968	0.0520	A\$57,062
10	A\$4651	0.0774	A\$60,056
Response rate			
Use per-cycle response rates (not average) + LOCF ^a	A\$8624	0.1450	A\$59,461
Upper 95% CI (0.7915 after first injection, and 0.8685 thereafter)	A\$6593	0.1103	A\$59,770
Lower 95% CI (0.5784 after first injection, and 0.7843 thereafter)	A\$3221	0.0537	A\$59,989
Apply response after treatment stoppage in the current PBS regimen, based on placebo response of 36% ^b	A\$4533	0.0677	A\$66,967
Treatment discontinuation (despite response), incobotulinumtoxin-A			
5% per cycle	A\$3115	0.0519	A\$59,988
10% per cycle	A\$2172	0.0362	A\$60,027
Disease natural resolution			
5% per cycle	A\$4329	0.0722	A\$59,934
10% per cycle	A\$4134	0.0690	A\$59,954
Cost inputs			
Plus A\$100 per treatment cycle	A\$4929	0.0757	A\$63,647
Minus A\$100 per treatment cycle	A\$4262	0.0757	A\$56,329
Apply 14.14 weeks between injections as per the observed dose intensity under an ‘as needed’ regimen ^c (apply 84.9% to the treatment cost)	A\$3848	0.0757	A\$50,865
Utility inputs			
Upper 95% CI values for the ‘in response’ value (0.55)	A\$4533	0.1009	A\$44,933
Lower 95% CI values for the ‘in response’ value (0.47)	A\$4533	0.0504	A\$89,867
Discounting rate			
3.5%	A\$4654	0.0776	A\$60,005
No discounting	A\$4963	0.0824	A\$60,226

All outputs discounted at 5% per annum

ICER incremental cost-effectiveness ratio, LOCF last observation carried forward, QALYs quality-adjusted life-years, CI confidence interval, PBS Pharmaceutical Benefits Schedule, SoC standard of care

^a0.6849/0.7917/0.8539/0.9206/0.9211 for the first/second/third/fourth/fifth treatment cycles, respectively

^bThirty-six percent of responders at the fourth treatment cycle remain in response after the treatment stoppage (while receiving SoC alone). This response rate is successively applied to those in response in the subsequent treatment cycles. This rate is based on the placebo-controlled, double-blind study by Kaňovský et al. [11]

^cThe extension study [11] employed a flexible ‘as needed’ re-injection interval design with a minimal interval of 12 weeks. The mean re-injection interval observed under this trial protocol was 14.14 weeks

utility score of 0.39 prior to treatment; an effective treatment with incobotulinumtoxin-A offered a utility gain of 0.12. This utility gain for being a responder to treatment is assumed to be constant over the model horizon as long as the patient maintains response. This could potentially be a conservative assumption as a sustained response may provide further mobility improvement, although evidence is lacking to inform the modelling of this potential long-term benefit.

A modelled CUA of onabotulinumtoxin-A previously reported in the literature [21] reported similar results to this analysis of the long-term use of BoNT-A for PSS-UL. The Scottish study reported ICERs ranging from £10,720 to £27,134 per QALY gain when compared with SoC alone over 5 years.

The main limitation of this current study is its reliance on the post hoc analysis of response rates reported in the extension study, and the assumption that these rates will remain constant in the long-term. These post hoc analyses are

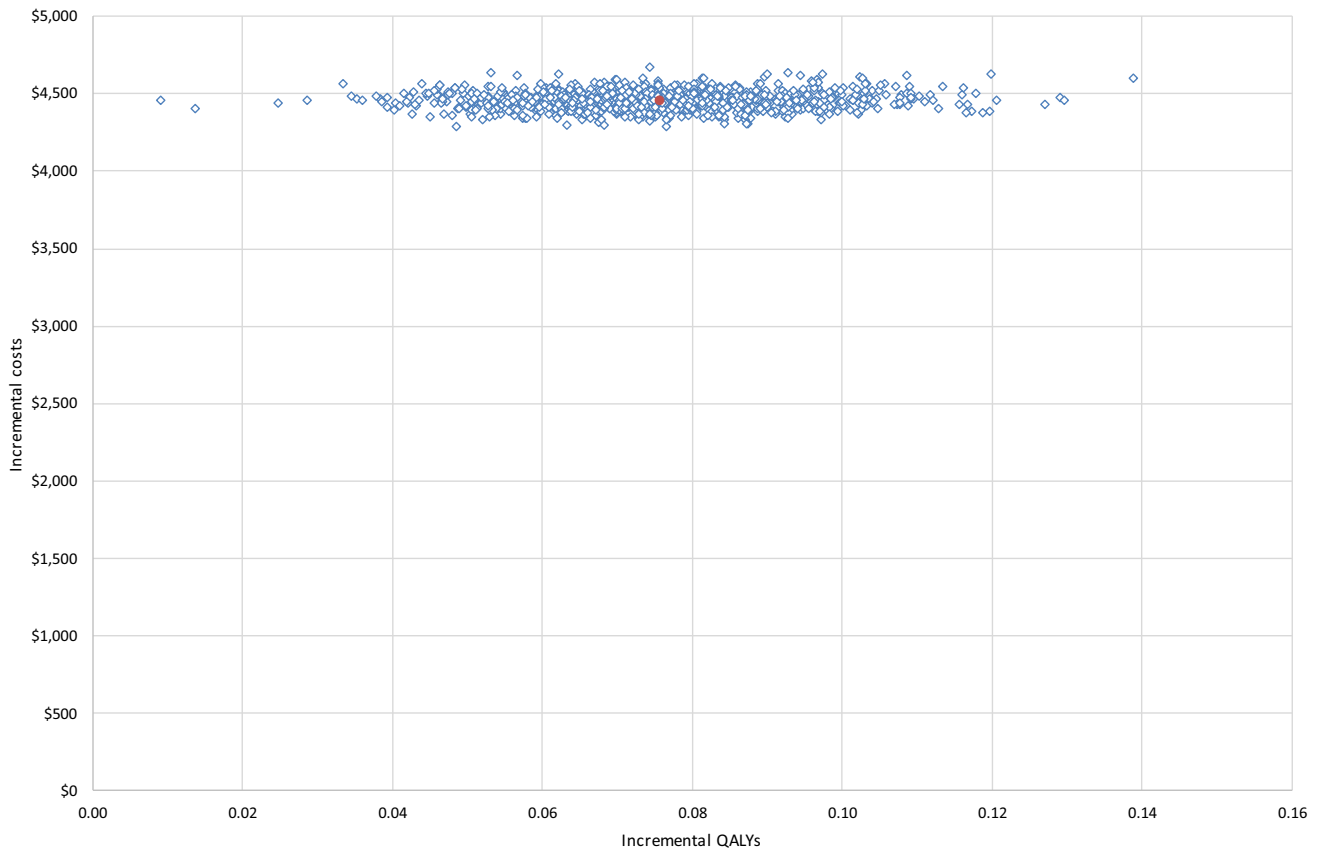
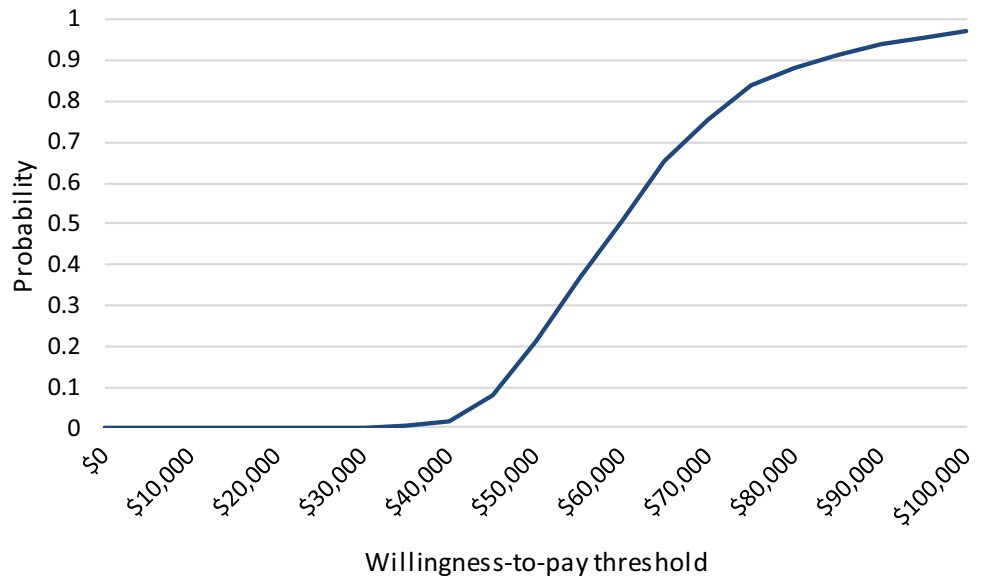


Fig. 3 Scatterplot for PSA for the extended incobotulinumtoxin-A regimen versus the current PBS-subsidised regimen of incobotulinumtoxin-A (maximum of four treatment cycles). Red dot

represents the base case. *PSA* probabilistic sensitivity analysis, *PBS* Pharmaceutical Benefits Scheme, *QALYs* quality-adjusted life-years

Fig. 4 Cost-effectiveness acceptability curve for the extended incobotulinumtoxin-A regimen versus the current PBS subsidised regimen of incobotulinumtoxin-A (maximum of four treatment cycles). *PBS* Pharmaceutical Benefits Scheme



consistent with clinical practice that demonstrate incobotulinumtoxin-A treatment continues to be effective beyond the current restriction of four injections [12]. In addition, these analyses suggested that the likelihood of achieving a

treatment response was more favourable among patients with response to previous treatment cycles. However, it must be acknowledged these analyses do not necessarily prove incobotulinumtoxin-A will continue to be effective in the

long-term, as the model assumes. Sensitivity analysis showed this long-term response rate was not an important determinant of cost effectiveness, due to the fact that incremental costs and incremental QoL gains would both decline with declining long-term response rates.

Furthermore, the model assumes that all four treatments are administered to patients in four sequential cycles every 12 weeks. However, patients may, in clinical practice, opt for longer re-injection intervals as the restriction is limited to a maximum of four treatment cycles per upper limb per lifetime. The current model assumes an approximation of strictly 12-weekly treatment cycles and is unlikely to meaningfully affect the base-case conclusion.

The model also assumed that upon treatment discontinuation, the severity of spasticity returned to the baseline level. This assumption was necessary because the natural history of the condition is only partially understood [7]. It is possible that some patients could experience resolution of their spasticity with or without treatment because of the natural course of the condition [22], however this could be expected to be small. It is nonetheless acknowledged that this is an area of uncertainty, potentially favouring the treatment arm of the model. On the other end of the spasticity continuum, some patients would not achieve resolution and thus require ongoing treatment cycles to maintain the alleviation of muscle tone and functional ability.

The model assumed no differences between the treatment arms in terms of safety and adverse events and omitted potential cost and QoL implications associated with treatment-related adverse events. This assumption is clearly supported by the available RCT evidence. Kaňovský et al. [11] suggested treatment tolerability was ‘good’ or ‘very good’ in 97% of patients, with no differences between incobotulinumtoxin-A and placebo, and most adverse events were mild and transient. Similar results were also reported by Elovic et al. [13]. The extension phase data also supported the treatment’s favourable tolerability, with none of the reported adverse events having been considered as being treatment related [12]. For the current comparison of continuing versus stopping incobotulinumtoxin-A after four treatment cycles, this assumption should be considered as adequate.

The current study had a narrow scope in capturing healthcare resource use, where only those costs directly associated with the provision of injections (i.e. drug acquisition and administration costs only) were included. This is a conservative approach, biasing against the extended treatment arm of the model. The management of moderate to severe PSS-UL can be resource-intensive and the maintained functional ability through ongoing treatment could provide cost savings to the healthcare system. Observational data reported by Baeten et al. [23] and Lundstrom et al. [24] have suggested the extent of this potential cost saving is more

substantial. A detailed analysis of the resource utilisation and costs of PSS-UL in patients with and without response to treatment would further improve the reliability and applicability of these results.

A key feature of this analysis is that it represents a circumstance unique to Australian clinical practice. That is, the Australian reimbursement system limits treatment to only four injections regardless of response or a demonstrated clinical need for continued treatment. Our analysis demonstrates that incobotulinumtoxin-A is effective beyond four injections when used in patients who are ‘known responders’. The incremental cost per QALY gained of A\$59,911, as estimated in this study, is relatively high but consistent with other treatments that have achieved PBS listing [25, 26].

5 Conclusion

Continuing incobotulinumtoxin-A treatment beyond four cycles may be cost effective. Careful patient selection is required so treatment is targeted at those with the greatest likelihood of continuing to respond to multiple treatment cycles.

Author contributions KM helped design the research question and model structure, developed the economic model and generated the results, and wrote and reviewed drafts of the manuscript. DT helped design the research question and model structure, and wrote and reviewed drafts of the manuscript. CG and MM extracted clinical trial data and collected other inputs for the economic analysis, and wrote and reviewed drafts of the manuscript. IJB provided clinical expert opinion on the disease area of PSS, which helped design the research question and model structure, and reviewed drafts of the manuscript.

Compliance with Ethical Standards

All authors have disclosed any possible conflicts of interest. Dominic Tilden is the sole owner and Director of THEMA Consulting. Koji Makino, Carmel Guarnieri and Mia Mudge are employed by THEMA Consulting, which was paid consulting fees from Merz Pharmaceuticals to conduct research and analysis, and the writing/preparation of this manuscript. Throughout his career as a rehabilitation specialist, Ian J. Baguley has received honoraria from Allergan, Ipsen and Merz related to speaking and advisory board activities for BoNT-related activities.

Data Availability Statement The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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