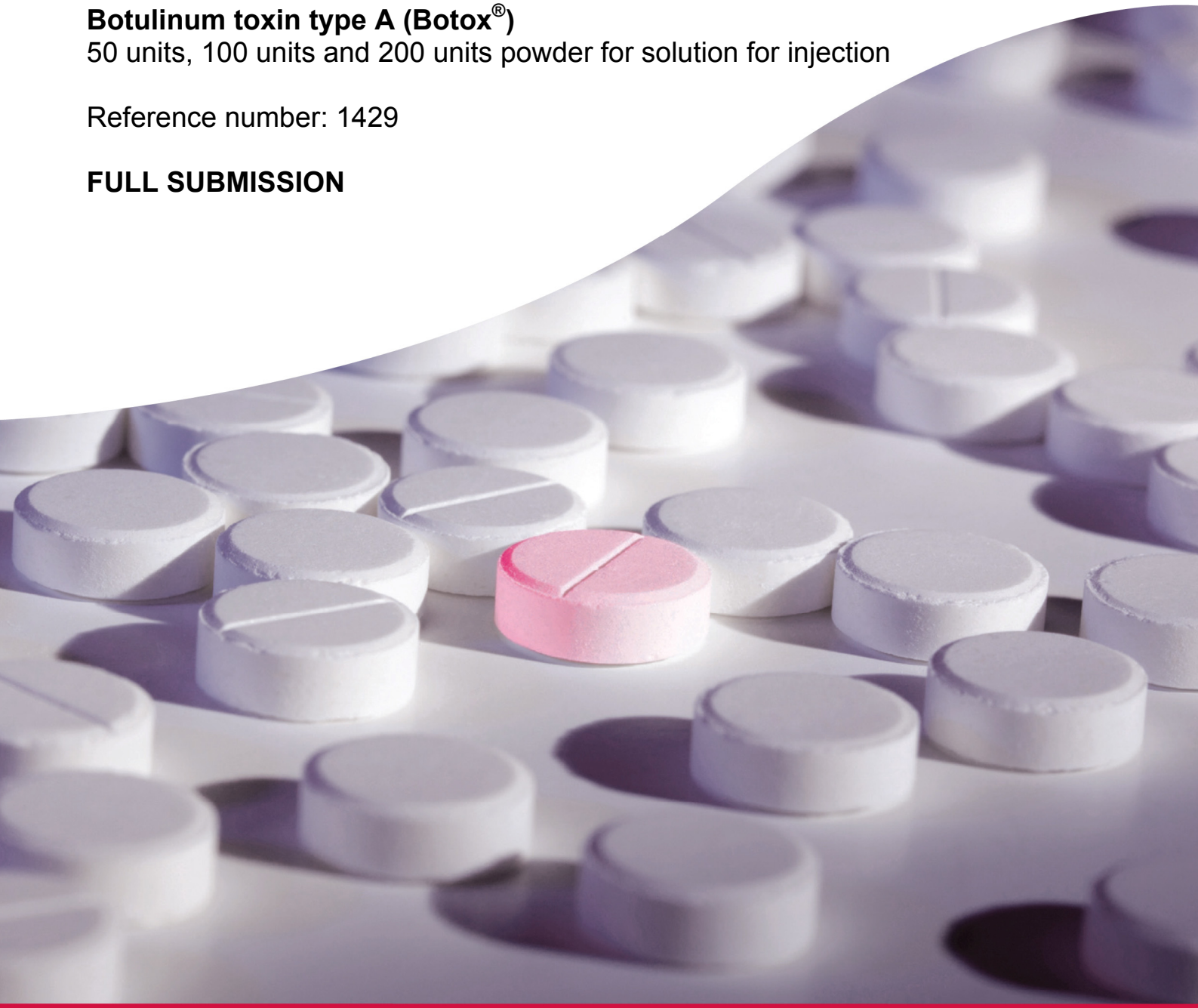
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Botulinum toxin type A (Botox®)
50 units, 100 units and 200 units powder for solution for injection

Reference number: 1429

FULL SUBMISSION



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics and Medicines Evaluation, Bangor University.

Please direct any queries to AWTTC:

All Wales Therapeutics and Toxicology Centre (AWTTC)
University Hospital Llandough
Penlan Road
Llandough
Vale of Glamorgan
CF64 2XX

awttc@wales.nhs.uk
029 2071 6900

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AWMSG Secretariat Assessment Report
Botulinum toxin type A (Botox®) 50 units, 100 units and 200 units powder for solution for injection

This assessment report is based on evidence submitted by Allergan Ltd on 27 June 2013[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Botulinum toxin type A (Botox®) for the management of urinary incontinence in adult patients with neurogenic detrusor overactivity due to subcervical spinal cord injury (traumatic or non-traumatic) or multiple sclerosis, who are not adequately managed with anticholinergics; patients should be already catheterising or willing and able to catheterise if required[2].
Dosing	The recommended dose is 200 units of Botox®, as 1 ml (approximately 6.7 units) injections across 30 sites in the detrusor muscle. Patients should be considered for re-injection when the clinical effect of the previous injection has diminished, but no sooner than three months from the prior bladder injection. Botulinum toxin units are not interchangeable from one product to another. Doses recommended in Allergan units are different from other botulinum toxin preparations. Refer to the Summary of Product Characteristics (SPC) for further dosing information[2].
Marketing authorisation date	24 September 2012[2]

2.0 DECISION CONTEXT

2.1 Background

The urinary tract has two main functions: to store and expel urine. These functions are controlled and regulated by the central and peripheral nervous systems. Neurological disease resulting in damage to the brain, suprasacral spinal cord, sacral spinal cord or peripheral nervous system can lead to bladder and sphincter dysfunction. A dysfunction in bladder function control may result in neurogenic detrusor overactivity (NDO); this mainly affects urine storage, particularly in patients exhibiting a loss of upper motor neurone control, for example in spinal cord injury (SCI) and multiple sclerosis (MS). Symptoms of impaired urine storage include increased frequency of urination and urinary incontinence[3,4]. NDO has a significant impact on the lives of patients, affecting physical (e.g. infections and sores), economic (e.g. use of incontinence pads and hospitalisation) and psychological (e.g. decreased socialisation and depression) aspects[4].

In order to reduce the frequency of urinary incontinence episodes, patients with incontinence due to NDO often use clean intermittent catheterisation (CIC) to mechanically empty the bladder, although urinary incontinence between catheterisations may still commonly occur. The pharmacological approach involves the use of anticholinergics; however, therapy may be limited due to inadequate efficacy and side effects such as dry mouth, constipation and cognitive defects. These effects may be compounded in patients with neurological impairment, such as MS or SCI.

Other therapies include invasive surgical procedures, which may also have efficacy limitations and have an associated inherent risk; therefore, these are frequently considered as a last-line option[4].

The National Institute for Health and Care Excellence (NICE) Clinical Guideline (CG) 148 suggest the following treatments to improve bladder storage; behavioural therapy including timed voiding, bladder retraining or habit retraining; antimuscarinics; botulinum toxin type A, and surgical options such as augmentation cystoplasty[3]. Botox® is a protein complex, consisting of neurotoxin type A, derived from *Clostridium botulinum*. This complex inhibits peripheral acetylcholine release at presynaptic cholinergic nerve terminals. Following intradetrusor injection, Botox® affects the efferent pathways of detrusor activity through this inhibition of acetylcholine release. Additionally, Botox® inhibits afferent neurotransmitters and sensory pathways[2]. In doing so, treatment with Botox® reduces detrusor pressure during the filling phase of the bladder therefore reducing urinary incontinence episodes[4].

2.2 Comparators

The comparator included in the company submission was best supportive care (BSC).

2.3 Guidance and related advice

- NICE. Urinary incontinence in neurological disease. Clinical Guideline 148. (2012)[3].
- Scottish Intercollegiate Guidelines Network (SIGN). Management of urinary incontinence in primary care. (2004)[5].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included details of two pivotal phase III trials, studies 515 and 516, which described the efficacy and safety of Botox® for the treatment of urinary incontinence. Due to their similar design, studies 515 and 516 will be described together, with results presented as a pooled analysis. Two doses of Botox® (200 units and 300 units) were investigated in these studies; however, the licensed dose for the indication under consideration is 200 units. Therefore, results pertaining to the Botox® 300 units dose will not be discussed further. In addition, the company has provided data from an extension study of studies 515 and 516 (study 094); interim efficacy results have been used to support longer-term outcomes. The applicant company also provided information on two phase II trials, 511 and 518. The efficacy results of these trials will not be discussed; however, safety data have been included in a pooled analysis.

3.1 Comparative efficacy

3.1.1 Studies 515 and 516

Studies 515 and 516 were randomised, multicentre, double-blind, placebo-controlled phase III trials, which assessed the efficacy and safety of Botox® versus placebo in adult patients (≥ 18 years) with ≥ 14 urinary incontinence episodes per week due to NDO from SCI or MS, who have not been adequately managed with anticholinergic therapy (defined as an inadequate response or intolerable side effects after at least one month of anticholinergic therapy on an optimised dose)[1,4,6,7]. Patients (n = 468) were randomised to receive Botox® 200 units plus BSC (n = 227) or placebo plus BSC (n = 241). BSC encompasses behavioural therapy, incontinence pads alone or in combination with CIC, and possible anticholinergic medication. Patients who were previously receiving anticholinergics continued to do so at a stable dose for the study duration and patients who did not perform CIC at baseline had to be willing to initiate CIC if required. After at least 12 weeks from initial treatment, patients were eligible for retreatment if they met the prespecified criteria: patients had to have requested retreatment and achieved a predefined threshold for frequency of weekly urinary

incontinence episodes that indicated a return of symptoms (50% reduction from baseline in study 515 and 30% in study 516). Patients who received only one treatment were followed for up to 52 weeks after randomisation ; if a second treatment was received, patients were followed up for at least 12 weeks (maximum follow up 64 weeks after randomisation)[1,4].

The primary endpoint was the change from baseline in the number of weekly urinary incontinence episodes six weeks after the first treatment. When compared to placebo, urinary incontinence episodes statistically significantly decreased with Botox® (−21.3 [32.4 at baseline] for Botox® versus −10.5 [31.5 at baseline] for placebo, $p < 0.001$). This statistically significant decrease was maintained at week 12. In addition, patients in the Botox® arm also demonstrated significant improvements in urinary continence: at 12 weeks, 35.7% of patients receiving Botox® had a 100% reduction in urinary incontinence episodes compared to 7.5% of patients receiving placebo ($p < 0.001$)[4]. Subpopulation analyses by aetiology (MS and SCI) and results from additional analyses supported these findings[1,4]. Patients receiving Botox® showed an increase in the number of weekly voids by CIC compared to placebo; these results were not statistically significant between treatment groups[1]. Quality of life was analysed using the Incontinence Quality of Life Questionnaire (I-QoL); this was a validated, disease-specific, self-administered questionnaire, designed to measure the impact of urinary incontinence on patients' lives. Statistically significant improvements in quality of life were reported at six and 12 weeks in patients receiving Botox® versus placebo[1]. Refer to Table 1.

In studies 515 and 516, 58% and 50% of patients received a second treatment with Botox®. Following retreatment, statistically significant decreases in the frequency of urinary incontinence episodes were observed from baseline (defined as the data collected prior to the most recent study treatment) at six and 12 weeks post retreatment (study 515: −15.3 and −16.4 [$p < 0.001$]; study 516: −22.1 and −18.9 [$p < 0.001$])[4].

3.1.2 Study 094

Study 094 was a prospective, long-term, open-label, extension study of the phase III trials, 515 and 516, which was designed to assess the efficacy and safety of repeat treatments with Botox® 200 units in patients (n = 202) with urinary incontinence due to NDO resulting from SCI and MS. After repeat treatments of Botox®, similar reduction in the number of weekly urinary incontinence episodes was observed to studies 515 and 516[8].

Table 1. Pooled results of studies 515 and 516[1,4]

	Pooled results from studies 515 and 516				
	Botox® 200 units		Placebo		p value
Primary endpoint	**n**	**Mean (SD)**	**n**	**Mean (SD)**	
Change from baseline in the number of weekly urinary incontinence episodes to week 6	227	−21.3 (21.60)	241	−10.5 (17.83)	p < 0.001
Additional analyses	**n**	**Mean (SD)**	**n**	**Mean (SD)**	
Change from baseline in the number of weekly urinary incontinence episodes to week 12	223	−20.6 (20.99)	228	−9.9 (18.28)	p < 0.001
Change from baseline in the number of weekly voids by CIC to week 6	212	2.2 (11.59)	220	0.1 (8.42)	p = 0.464
Change from baseline in the number of weekly voids by CIC to week 12	205	2.6 (12.68)	215	0.4 (9.43)	p = 0.311
Change from baseline in I-QoL outcomes to week 6	220	25.89 (26.20)	226	11.15 (19.06)	p < 0.001
Change from baseline in I-QoL outcomes to week 12	213	28.89 (25.94)	219	8.86 (19.55)	p < 0.001
CIC: clean intermittent catheterisation; I-QoL: Incontinence Quality of Life Questionnaire; MS: multiple sclerosis; SCI: spinal cord injury; SD: standard deviation					

3.2 Comparative safety

The comparative safety of Botox® 200 units versus placebo is reported in studies 515 and 516; however, the company has pooled data from these studies with evidence from two phase II studies, 511 and 518[1,4]. The incidence of treatment-related adverse events (AEs) was higher in the Botox® 200 units arm than in placebo following first treatment (32.1% for Botox® versus 16.2% for placebo). The most frequently reported AEs in ≥ 3% of patients were urinary tract infection (UTI: 49.2% in the Botox® arm versus 35.7% in the placebo arm) and urinary retention (17.2% versus 2.9%)[1,4]. In the Botox® 200 units arm, 2.3% of patients discontinued from the studies due to AEs; this figure was 1.1% in the placebo arm[4]. The overall profile of AEs was similar in patients receiving repeated doses of Botox®. The majority of AEs were considered to be mild or moderate in severity and there was no increase in the incidence of AEs[1]. No unexpected new AEs were observed in patients exposed to multiple treatments of Botox®[1].

In MS patients, the most frequently reported serious AE (SAE) was MS relapse, occurring in 1.5% of patients in the Botox® 200 units arm versus 4.5% in the placebo arm. In SCI patients, the most frequently occurring SAE was urinary tract infection, reported in 0.8% of patients in Botox® arm versus 2.2% in the placebo arm[4].

3.3 AWTTC critique

- Treatment with Botox® in addition to BSC compared to BSC alone had a positive effect on reducing the number of weekly urinary incontinence episodes. Across the two pivotal studies, the median duration of treatment effect following treatment with Botox®, measured as the time to patient request for retreatment, was 38.4 weeks. Treatment with Botox® was also shown to have a quick onset of action; effects were reached within two weeks and maximum effects within six weeks. The company state that treatment with Botox® resulted in clinically meaningful benefits versus BSC. Botox® treatment was also associated with a significant improvement in quality of life[1].

- There are limited efficacy and safety data available for the management of urinary incontinence in adult patients with NDO as a result of SCI or MS beyond two treatment administrations. The Medicines and Healthcare products Regulatory Agency (MHRA) state that a clinically relevant effect can be estimated to last for approximately 10 months, but experience after repeated treatment dose is limited. However, interim results from study 094 show that the number of weekly urinary episodes decreased after repeated treatment with Botox®; the results were supportive of studies 515 and 516[8]. The MHRA also state that a strategy of anticholinergics dose reduction and its impact on the efficacy and safety of Botox® needs to be evaluated in the long term; 55% of patients in studies 515 and 516 were receiving anticholinergic therapy at baseline. However, the MHRA note that a therapeutic effect has been demonstrated regardless of the combined use of anticholinergics[4].
- NICE CG148 outlines guidance for the management of urinary incontinence associated with neurological disease; this includes behavioural therapy, antimuscarinics, botulinum toxin type A and surgical options[3]. In their submission, the applicant company provided comparator evidence for the use of Botox® with BSC versus BSC alone. No comparative clinical effectiveness data have been provided between Botox® and surgery. The applicant company state that surgery would usually only be an option when all other treatments have failed. The applicant company note that, although not as invasive as surgery, a proportion of patients may not wish to undergo the administration procedure for Botox® treatment[1].
- In the pivotal clinical trials, UTIs and urinary retention were found to be the most prevalent AEs in both aetiological subgroups; however, they were reported in a greater proportion of MS patients than SCI patients (urinary tract infection: 53.0% of MS patients versus 45.4% SCI patients; urinary retention: 28.8% MS patients versus 5.4% SCI patients). The company suggest that this increase may have resulted from a greater proportion of patients who initiated CIC during these studies; CIC was more common in SCI patients than in patients with MS (CIC at baseline: 32.0% of MS patients versus 85.8% SCI)[1,4].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submitted a cost-utility model comparing Botox® 200 units plus BSC versus BSC alone for the management of urinary incontinence in adult patients with NDO due to SCI or MS, who are not adequately managed with anticholinergics. Subgroup analyses are provided for patients with MS and SCI[1].

Patients entering the model are assumed to have the same characteristics as those enrolled in the two clinical trials. The assumed usage of pads, CIC and medication in the model mirrors usage in the pooled clinical trials (studies 515 and 516)[6,7]. The Markov model has six-weekly cycles, a five year time horizon, adopts an NHS perspective and 3.5% discount rates[1]. The treatment-related outcomes are the same as those in the clinical trials[6,7]. Outcomes of the first treatment at weeks six and 12 are taken from the pooled results of the clinical trials[6,7]. After 12 weeks, patients in the trials' placebo arms could cross-over to active treatment, therefore making direct comparisons between groups difficult to interpret. A loss of efficacy between Botox® treatments, the factor prompting a request for retreatment, is modelled using a time-dependent weighting of utility scores. Retreatments are assumed to have similar efficacy to the first treatment, such that patients who respond are maintained in their week 12 health states for the remainder of the modelled time horizon. Nonresponders receive no further treatment with Botox® but continue to receive BSC.

After three years, nonresponders are considered for augmentation cystoplasty, with 5% receiving surgery. Post-surgery, 78% achieve dryness and 17% benefit from a 50–99% reduction in urinary incontinence frequency. Those not receiving surgery remain on BSC.

Efficacy of BSC in clinical practice is assumed to be no greater than the efficacy of placebo injections in the pooled BSC groups from the trials[6,7]. UTIs (symptomatic and asymptomatic) are modelled as AEs, with rate as at week 12 of the pooled trials[6,7].

Administering Botox® is costed as a day case (£292)[9] plus medicine (£276.40). Administering BSC is by an outpatients' appointment (£103)[9]. Nonresponders see a urologist every three months, reducing to every six months for responders (£102 each)[9]. Augmentation cystoplasty cost £5,847[9]. Other costs include the anticholinergic oxybutynin (£11.60 per month)[10], incontinent pads (£0.25 each)[3] and CIC (£0.75 each)[3].

Utilities are generated directly from the Incontinence Quality of Life Questionnaire (I-QOL). The 22-item questionnaire was reduced to five items with three levels of response. Preferences were elicited from 440 UK participants and the results extrapolated and recalibrated to a scale ranging from 0 to 1 to provide utilities. The utility for dry health state is 0.562, non-dry responder 0.435 and nonresponder 0.240. Utilities for MS health states exceeded those for SCI, particularly for those in dry state (0.607 versus 0.481).

4.1.2 Results

Table 2 presents the base case results, with an incremental cost-effectiveness ratio (ICER) of £3,850. MS patients have a higher ICER than those with SCI (£6,422 versus £1,767).

Table 2. Results of the base case analysis per patient over five years

	Botox® + BSC	BSC	Difference
Study treatment and administration costs	£3,038	£205	£2,833
Other healthcare costs (outpatients, pads, CIC, medicines, surgery, UTIs)	£5,697	£6,841	−£1,144
Total NHS costs	£8,735	£7,046	£1,689
Total life-years	4.42	4.42	0
Total QALYs	1.7236	1.2848	0.4388
ICER (£/QALY gained)	**£3,850**		
QALY: quality-adjusted life-year			

Probabilistic sensitivity analysis indicates that at cost-effectiveness thresholds of £20,000 and £30,000 per QALY, Botox® is cost-effective compared to BSC in 100% of iterations.

The company presented extensive sensitivity analyses often using the standard error (SE) associated with the parameter value as a measure of uncertainty; costs are varied by 10%. Results indicate the ICER is sensitive to:

- Time horizon, with a shorter time horizon increasing the ICER;
- Urologist attendances by nonresponders, with the ICER increasing as these reduce;
- Time between Botox® treatments, with the ICER reducing as periodicity lengthens;
- Utility values;
- Clinical efficacy, particularly the proportion of non-dry responders in BSC;
- Use of CICs in the BSC arm;
- Adopting one urodynamic assessment for patients treated with Botox® who are non-dry or nonresponders after the first treatment;
- Administration costs.

Results for these scenarios and sensitivity analyses are presented in Table 3. In the other sensitivity analyses, the ICER did not exceed £4,000.

Table 3. Results of sensitivity and scenario analyses presented by the company

Scenarios	ICER	Plausibility
Base case	£3,850	The costs and associated efficacy of Botox® are potentially too high; base case assumes all patients receive five treatments. Utility values are inconsistent with those adopted in other studies
Time horizon: 12 weeks and one year	£18,737 and £6,737	Limited: responders expected to request repeat treatments
Urologist attendances in nonresponder patients two not four a year	£4,677	Plausible: if urologist has no treatment options then regular visits unlikely
Urodynamic assessment in non-dry and nonresponders	£4,173	Judged unlikely in all settings for such patient groups
Time between Botox® treatments 7.2 months and 11.3 months	£5,194 and £2,739	Longer time intervals (> 11.3 months) are plausible in NHS services
Varying utility values within SE range	£4,005 and £3,707	SEs are small (maximum 2% from base case); uncertainty is greater
Same deterioration profile in each arm between treatments	£4,737	Different profiles probable
Apply SE to estimate % of patients at week 12 across health states	£3,715 to £4,233	Uncertainty greater than SEs at week 12 measures, particularly in the longer term
Mean CIC use ±10% per month in BSC arm nonresponders	£3,296 to £4,405	Base case assumes five CIC a day so +10% per person unlikely but may be increase in CIC users in Botox® arm with repeat treatments
One urodynamic assessment for non-dry or nonresponders after first treatment cycle with Botox®	£4,173	Judged unlikely to occur in all settings
Cost of Botox® administration ±10%	£3,507 to £4,194	Range of cost for day cases expected to be wider than 10%

4.1.3 AWTTC critique

Key issues within the economic evaluation which may lead to an understated ICER are:

- Choice of utility values
- Understatement of UTIs and other AEs in the Botox® arm
- Overstatement of administration costs in the BSC arm

However, some factors may cause the ICER to be lower than the base case value:

- Assumed equivalence between a placebo effect from injections of 0.9% sodium chloride and BSC in clinical practice. The placebo arm achieved results which may not be matched in practice with almost 40% of patients achieving a > 50% reduction in urinary incontinence at 12 weeks.
- Retreatment is provided on request with no wait. Increasing the period from 8.9 months to 11 months reduced the cost/QALY by £1,000 from £3,850 to £2,849.

There is also considerable uncertainty arising from absence of long-term safety and efficacy data after repeat treatments from clinical trials: no efficacy data in less severe patient groups; no comparative data after week 12 and the discontinuation rate.

Sensitivity of results has been tested using alternative values (described later in this section) for the efficacy parameters and an eleven month retreatment period. The ICER remains under £10,000. Longer term data must await publication of results from extension study 094[11]. On the basis of available data and despite several weaknesses in the submitted evaluation, on balance, Botox® plus BSC seems likely to have a cost/QALY of under £20,000 compared to BSC for these patient groups, with this level

of disease severity and no retreatment unless a patient achieves a 50% reduction in urinary incontinence episodes.

Strengths of the economic evidence include:

- Patient groups and indications in the model reflect those in the clinical trials and the licensed indication. Subgroup analyses for MS and SCI patients are provided.
- Comparator and associated treatment pathways are consistent with those recommended in NICE CG148[3] and follow consultation with five Welsh experts, including two consultant urologists[1].
- Baseline and clinical efficacy data come from studies 515 and 516 for the first treatment period[6,7].
- Unit costs from appropriate sources.
- Extensive sensitivity and scenario analyses.
- The model, developed in Microsoft® Excel, is clearly set out with good labelling and well-presented sensitivity and scenario analyses.
- Most assumptions were referenced and could be validated.

Weaknesses include:

- 'Inadequately managed' on anticholinergics is not defined which may give rise to variation in using Botox® in clinical practice; use may not be limited to patients with severe urinary incontinence i.e. similar to those in the clinical trials.
- The assumption that BSC in clinical practice has comparable efficacy to placebo injections in the phase III trials[6,7] could not be validated.
- The MHRA note that no long term safety and efficacy data after repeat treatments are available[4]. At publication, 113 patients had completed three treatments but the rate of missing data was 26%[4].
- Loss in efficacy between Botox® treatments was not associated with increased use of incontinence pads which favours the Botox® arm.
- Modelled annual discontinuation rate of 3% for the Botox® arm seems inconsistent with the pooled study data which indicate about 47% of patients completed the second treatment, equivalent to 55% when adjusted for factors such as lost to follow-up and protocol violations.
- Model assumes retreatment will be available on request, subject to meeting efficacy criteria, at 12 weeks after the previous treatment. The MHRA noted almost 50 protocol violations in respect of retreatment suggesting rates and times are uncertain[4]. In clinical practice, a delay between request and retreatment is almost inevitable. A longer time interval between treatments reduces the ICER.
- Utilities obtained using the I-QOL are materially different from those used in the model informing the NICE CG148. The values used in the NICE model were 0.66 for incontinence (five episodes of urinary incontinence a day), 0.75 for mild incontinence (two episodes of urinary incontinence a day) and 0.78 for dry[3]. In comparison the values used in this submission ranged from 0.25 to 0.61.
- The model attributes no cost for patients requiring CIC because of treatment. The MHRA noted 40% to 50% of MS patients started using CIC after Botox® treatment[4]. No additional costs were included for these patients although the Summary of Product Characteristics (SPC) notes they should be assessed two weeks post-intervention and periodically thereafter.
- Using SEs to measure parameter uncertainty understates the uncertainty associated with certain variables, particularly utility values.
- The model may understate cost of AEs for several reasons including:
  - The model includes only UTIs at week 12 of the clinical trials[6,7]. Other relevant events are urinary retention (17.2%), haematuria (5%) and MS relapse (1.5%)[1].

  - In the Botox® arm of the trials, UTIs increased from 24% at week 12 to 49% at the end of the first treatment. The increase in UTI rates is greatest in those who initiated CIC post-treatment, suggesting there may be an impact of CIC on UTI rates[8].
  - All UTIs are managed by one course of medication, with none being moderate to severe. However, some UTIs detected in urine may not subsequently become symptomatic and hence not be treated.
- UTIs are managed by an urologist (£103) but a GP (£36[12]) is more appropriate.
- The model assumed administering BSC would require attendance at an outpatients' clinic (£103) in addition to three or six monthly monitoring (depending on status). This additional resource may not be appropriate for the Welsh setting.
- The number of free pads provided in Wales is 4 per day not 5[13]. Mean incontinence episodes per week for nonresponders in the Botox® arm was 36.7; payment for extra pads was not addressed.
- The sum of probabilities for health states of the comparator at week 12 is 0.968 not 1.

4.2 Review of published evidence on cost-effectiveness

A de novo economic model with a lifetime horizon was developed to inform recommendation in NICE CG148[3]. This compared Botox® to:

- Augmentation cystoplasty;
- Two treatments of Botox® followed by augmentation cystoplasty in nonresponders;
- BSC using a mixture of incontinence pads and catheters.

Base case analysis indicated that augmentation cystoplasty is the cost-effective option compared to Botox® and BSC assuming a lifetime horizon. Augmentation cystoplasty is cost-effective with a success probability of 78%. When Botox® is compared with BSC, the former is cost-effective with an ICER of under £9,000.

A second study compared cost-effectiveness of Botox® with standard care from the NHS perspective, concluding Botox® was highly likely to be cost-effective in neurogenic disease[14].

A third study, set in France, and hence with limited generalisability, compared Botox® to BSC and reported an ICER of 29,466 euro/QALY[15].

An American five-year cost analysis, with limited generalisability, comparing Botox® and augmentation cystoplasty, concluded that Botox® was cheaper at treatment durations of more than 5.1 months, but augmentation cystoplasty was cheaper if the augmentation cystoplasty complication rate dropped below 14%[16]. A cost comparison estimated five-year costs were $33,272 and $28,065 for augmentation cystoplasty and Botox®, respectively[17].

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Eligible patient: MS

The company applied data from a recent phenotypic study which estimated the prevalence of MS in Wales at 146 per 100,000 (4,473 people) and assumes 75% have NDO (3,355 people)[17]. A three-year prospective study[18], reported in 1989, measured incidence rates of 8.2 per 100,000 (251 people); of these 10% are assumed to have NDO (25 people). General population mortality rates for Wales of 0.59% are used to

derive an estimated population with MS and NDO of 3,360 in year one, rising to 3,380 at year five.

Of these patients, 65% are estimated to be bothered by their NDO (2,167 people), with 95% taking, or having taken, anticholinergics (2,059 people) but 50% are inadequately managed (1,029 people). The proportion willing to use a CIC if required is 32.2%, giving 332 patients eligible for treatment with Botox®.

Uptake rate for the medicine is estimated at 12.5% in year one, rising to 41% in year five, equivalent to 42 patients receiving treatment in year one and 137 in year five.

Eligible patient: SCI

The company applied prevalence data from a 1996 audit of patients attending a Centre for Spinal Injuries to estimate 1,500 prevalent cases of SCI in the Midlands and Wales. Adjusting for case-mix and relative populations results in an estimated 837 cases of SCI in Wales, with 92.4% of patients having NDO (773 people). Incidence rates are also from this audit, with 45 estimated incident cases of SCI and 41 with NDO. The same mortality rates are applied, giving 810 patients with SCI and NDO in year one, rising to 954 in year five.

All patients are assumed as bothered by NDO, with 95% taking or having taken anticholinergics (769 people) but 50% are inadequately managed (385 people). The proportion willing to use a CIC is 85.8%, giving an estimated 330 patients eligible for treatment with Botox®.

Uptake rate for the medicine is forecast to be 15% in year one, rising to 50% in year five, equivalent to 50 patients receiving treatment in year one and 194 in year five.

5.1.2 Results

Results of the base case analysis are presented in Table 4. Botox® is administered with BSC; relevant costs include anticholinergic medication, medication for UTIs, incontinence pads and CIC usage. Mean retreatment with Botox® is 253.2 days and 232.0 days for patients with MS and SCI, respectively.

In year one, total cost to manage 662 patients using Botox® plus BSC is forecast at £153,686. The higher costs are to manage patients with MS. In this group, medication costs per person are almost £400 higher and other costs (pads and CIC) are about £140 per person higher than BSC. This arises because of increased use of CIC in the Botox® arm following treatment.

By year five, additional cost to manage 723 patients with NDO using Botox® is almost £60,000. Patients with MS (334) have increased costs of £74,000 but there are savings of £14,000 from managing those with SCI (389) with Botox® plus BSC.

Table 4. Company-reported costs associated with use of Botox® and BSC for the treatment of NDO due to SCI or MS

	Year 1 (2013)	Year 2 (2014)	Year 3 (2015)	Year 4 (2016)	Year 5 (2017)
Eligible patients MS SCI	 332 330	 333 345	 333 360	 334 374	 334 389
Uptake (%) MS SCI	 12.5% 15.0%	 19.6% 23.8%	 26.8% 32.5%	 33.9% 41.3%	 41.0% 50.0%
Treated patients MS SCI Total	 42 50 92	 65 82 147	 89 117 206	 113 154 267	 137 194 331
Cost components Botox® treatment plus BSC					
Botox costs* MS SCI	 £16,746 £21,726	 £25,917 £35,631	 £35,486 £50,839	 £45,055 £66,916	 £54,625 £84,297
Total medication† MS SCI	 £20,008 £26,242	 £30,964 £43,036	 £42,397 £61,405	 £53,830 £80,824	 £65,263 £101,817
Non-medication costs§ MS SCI	 £35,147 £72,291	 £54,395 £118,556	 £74,479 £169,160	 £94,563 £222,655	 £114,647 £280,487
Total costs Botox® treatment plus BSC					
MS SCI Total	£55,154 £98,532 £153,686	£85,358 £161,592 £246,950	£116,875 £230,564 £347,439	£148,392 £303,477 £451,869	£179,908 £382,302 £562,210
Total costs BSC only					
MS SCI Total	£32,616 £102,087 £134,703	£50,477 £167,422 £217,899	£69,115 £238,882 £307,997	£87,752 £314,426 £402,178	£106,390 £396,096 £502,486
Net costs Botox® treatment plus BSC minus BSC only					
MS SCI Total	£22,538 -£3,555 £18,983	£34,881 -£5,830 £29,051	£47,760 -£8,319 £39,441	£60,639 -£10,949 £49,690	£73,518 -£13,793 £59,725

* Administration costs of £292 per dose are excluded.
† Botox® + anticholinergic + treatment for UTI. Administration and monitoring excluded.
§ Incontinence pads + CIC.

5.1.3 Scenario analyses

Three other scenarios are provided (Table 5). Scenario 1 includes cost per treatment to administer injections (£292) or provide BSC (£103). Under scenario 2 branded anticholinergic medications are considered rather than generic oxybutynin alone. With scenario 3, patients responding to Botox® stop taking anticholinergic medication after their first cycle of treatment.

Table 5. Company-reported scenario analyses for net costs

	Year 1(2013)	Year 2 (2014)	Year 3 (2015)	Year 4 (2016)	Year 5 (2017)
Base case	£18,983	£29,051	£39,441	£49,690	£59,725
Scenario 1	£35,904	£55,566	£76,082	£96,599	£117,115
Scenario 2	£18,014	£27,475	£37,206	£122,638	£56,057
Scenario 3	£15,332	£23,215	£31,261	£39,085	£46,574

5.1.4 AWTTC critique

The company has assumed no current use of Botox® treatment in Wales. It has also advised patients are already being treated with this intervention and therefore the actual net impact will be lower than that presented in the base case. Estimate of patients with MS came from two studies, both reporting definite and suspected/probable MS. Values used are the total. If patients with probable MS have a different treatment pathway then the number of potential patients may be overstated by about 12% (rate of 'probables' in the prevalence survey[17]). This study reported a higher incidence rate (9.65 per 100,000) compared to 8.2 as adopted in the submission.

Prevalence and incidence of SCI used audit data adjusted for case-mix between trauma and non-trauma patients. However, the resulting estimate of 2,050 patients exceeds the reported number of 1,500 which seems inappropriate. Estimated base case number of SCI may therefore be too high. The audit data are from 1996 and may not reflect current rates of SCI.

Budget impact base case excluded cost of administration, a day case cost of £292 per dose.

The company has suggested that the cost of BSC may be higher than estimated because the placebo effect, observed in the clinical trials, is unlikely to be replicated in clinical practice.

Forecast medication costs assume Botox® treatment is provided for one year only, with no retreatment in years two to five. Under the economic model some patients receive treatment for up to five years and clinical practice is likely to retreat responders beyond one year. The company budget impact analysis therefore underestimates resources and costs required to adopt the new treatment in future years.

The scenarios are helpful but a combination of all 3 aspects may better reflect likely clinical practice (i.e. some use of branded medication, administration costs but for injections only and not BSC and responders cease anticholinergic medication).

5.2 Comparative unit costs

The comparator in the economic model is BSC following failure of anticholinergic medication. However, the economic model included costs based on medication use by patients entering the clinical trials[1,6,7]. Oxybutynin hydrochloride is indicated for the management of urinary incontinence due to NDO. It is available as a generic, as a modified release (MR) formulation and as a transdermal preparation. Other anticholinergic medications may also be prescribed.

Table 6. Examples of acquisition cost of Botox® and oxybutynin hydrochloride for the management of urinary incontinence due to NDO

Treatment	Example dose*	Example cost per patient per year
Botulinum toxin type A (Botox®)	200 unit vial per treatment; treatment every three months***	£1,106
Oxybutynin hydrochloride (non-proprietary)	5 mg four times per day	£77.75
Oxybutynin hydrochloride MR (Lyrinel® XL)	20 mg once daily	£335.30
Oxybutynin patches (Kentera®)	One patch twice weekly	£2,484

* Doses based on relevant SPCs[2,19–23]
** Costs are based on current British National Formulary (BNF) list[10]
*** SPC advises re-injection should be no sooner than three months from the prior bladder injection. In clinical studies, the median interval between the first and second administrations was 42 weeks in patients with spinal cord injury and 45 weeks in patients with multiple sclerosis. Costs of administration are not included.
This table does not imply therapeutic equivalence of drugs or the stated doses.

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, botulinum toxin type A (Botox®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company do not anticipate that botulinum toxin type A (Botox®) will be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission highlighted ongoing studies that are likely to be available within 6–12 months:

- Study 094 (191622-094). Open-label extension study of patients enrolled in studies 515 and 516[11].
- Study 082 (191622-082). Phase II, placebo-controlled study in patients with urinary incontinence due to NDO and pre-existing respiratory impairment as a result of high cervical lesions[24].

6.3 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

6.4 Evidence search

Date of evidence search: 5 July 2013 and 8 July 2013
Date range of evidence search: No date limits were applied to database searches.

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