

Cost-effectiveness of Xeomin[®] in the management of cervical dystonia and blepharospasm

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ABSTRACT

Study objectives: Xeomin, a botulinum neurotoxin type A (BoNT/A), is licensed for the symptomatic management of blepharospasm (BP) and cervical dystonia (CD) of a predominantly rotational form (spasmodic torticollis) in adults. The objective of this study was to assess the cost-effectiveness of Xeomin from a UK NHS perspective.

Methods: A cost utility analysis (CUA) against placebo and cost minimisation analysis (CMA) against other BoNT/A were conducted. The CUA utilised a Markov model with six health states, a 3.5% discount rate per annum. Direct costs were assigned in 16 cycles with the effect on quality-adjusted life years (QALYs), using data from a prospective, open-labelled cohort study. Univariate sensitivity analyses were conducted.

Results: Xeomin was cost-effective versus placebo, with an incremental cost per QALY gained of GBP 6,441 in CD and GBP 3,734 in BP. Results held under sensitivity analyses. The CMA demonstrated in the majority of cases Xeomin represents the BoNT/A treatment with the lowest overall cost for CD and BP.

Conclusion: Xeomin is a cost-effective treatment option relative to placebo for patients with CD and BP. Xeomin demonstrated a similar efficacy and safety profile compared to other BoNT/A at a lower overall cost. Xeomin is the only BoNT/A treatment for CD or BP to be recommended by the Scottish Medicines Consortium (SMC) for use within NHS Scotland. Xeomin has the added benefits of i) not requiring cold chain storage, and ii) its potential lower immunogenicity. Xeomin represents a cost-effective treatment choice for patients with CD and BP in the UK healthcare system.

KEYWORDS

blepharospasm, botulinum neurotoxin, cervical dystonia, cost-effectiveness

INTRODUCTION

Cervical dystonia (spasmodic torticollis) is an idiopathic disorder characterised by involuntary posturing of the head, tilting and turning of the neck, and neck pain [1]. Blepharospasm is a progressive disease characterised by spontaneous, spasmodic, involuntary contractions of selected eye muscles [2]. Both conditions are chronic movement

disorders. If left untreated, they can impact a patient's ability to work, cause depression and pain, and reduce quality of life [3, 4]. The prevalence of all forms of dystonia is 0.0541%. For cervical dystonia (CD) the estimated prevalence is 0.0222%, while for blepharospasm (BP), estimated prevalence is 0.0043% [5]. Based on 2007 population estimates, the prevalence in Scotland equates to 1,137 patients for CD and 218 patients for BP.

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At present, botulinum neurotoxin Type A which includes Botox (BoNT/A complex, Allergan Inc, Irvine, CA, USA), Dysport (BoNT/A complex, Ipsen Ltd, Slough, UK), and Xeomin a BoNT/A treatment without complexing proteins (Merz Pharmaceuticals GmbH, Germany), is the standard pharmacological choice of care for CD and BP [6, 7]. Xeomin was found to be non inferior to Botox for both efficacy and tolerability in phase III clinical trials in both CD and BP and is indicated for the symptomatic management of BP and CD of a predominantly rotational form in adults [8].

No data on the cost-effectiveness of Xeomin has been published. A previous paper [9] had investigated the feasibility of attempting a cost utility analysis for dystonia treatments. The authors concluded that "The nature of

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the disease and its cyclical treatment caused practical difficulties in recruiting participants, administering questionnaires and in estimating QALY gains". The objective of this study was to therefore provide evidence of the cost-effectiveness of BoNT/A treatment in general, and of Xeomin in particular.

METHOD

Model

No other BoNT/A preparations besides Xeomin have gained approval by the Scottish Medicines Consortium (SMC) by showing data supporting an improvement in quality of life over placebo [10]. Placebo was therefore used as the comparator for this Xeomin cost effectiveness study. The economic evaluation however, did draw heavily upon historical data collected in Dysport and Botox-treated patients [3, 7]. A detailed literature search and review was not undertaken as one had recently been conducted within the literature as part of a Cochrane Review [10].

Xeomin was compared with Botox in patients with CD by means of a double-blind noninferiority trial, [11] in which 463 patients received intramuscular injections of 70 to 300 units Xeomin or Botox and were followed up for 16 weeks. All patients had a stable previous response to Botox therapy. The study demonstrated that Xeomin was at least as effective and well tolerated as Botox. In a double-blind phase III trial, the efficacy and toxicity profile of Xeomin and Botox in patients suffering from BP was compared [6]. Of 304 enrolled patients, 300 patients received study medication (intent-to-treat population), and 256 patients completed the study as planned (per-protocol population). Patients had to have been exposed to at least two previous Botox injections resulting in a stable response. At baseline, patients received a single injection of Xeomin or Botox (≤ 35 units per eye). No significant differences were found between Xeomin and Botox for all efficacy and safety variables 3 weeks and up to 16 weeks after injection. Both the Xeomin and the Botox group showed a decrease in the Jankovic Rating Scale sum score at week three, which signified an improvement in the symptoms of BP during this time period [6]. These data demonstrated that Xeomin was an effective and well tolerated treatment for patients suffering from BP and non-inferior to Botox.

To calculate the expected costs and health benefits in each treatment arm of the economic evaluation, a Markov state-transition model was constructed. This model comprised six health states and 16 cycles of 12 weeks for a time horizon of 3.5 years. We used published data, which followed 616 patients with CD treated with

Dysport for 16 cycles (12-week intervals) [7]. All costs and quality-adjusted life years (QALYs) were discounted at 3.5% per annum. Evidence of sustained efficacy over 16 cycles, incidence of adverse events (AEs), and rates of discontinuation due to lack of efficacy, AEs, secondary non-response, and satisfactory relief from the condition provided the transition probabilities for the BoNT/A arm of the model and were derived from Kessler et al [7].

The primary outcome measure used in the economic model was QALYs, which were considered appropriate for each of the economic evaluations as the objective of treating CD and BP was to improve a patient's quality of life. Further, the incremental cost per QALY ratio (ICER, GBP/QALY) calculated in the economic evaluation permitted comparison of the relative cost-effectiveness of Xeomin across different therapeutic areas.

The six health states of the Markov processes were as follows:

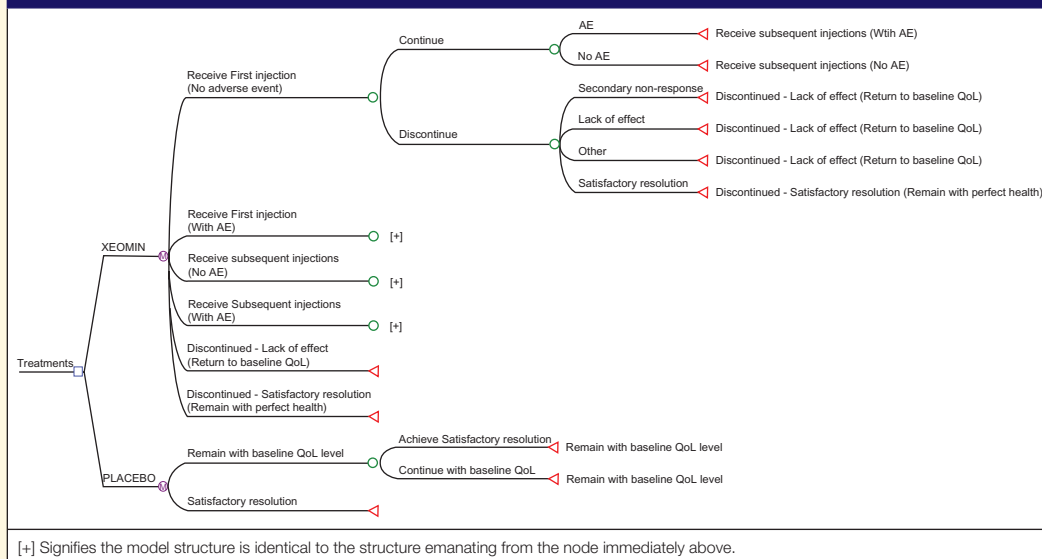
- Patient received their first injection with Xeomin and *did not* experience a significant AE that led to therapy discontinuation
- Patient received their first injection with Xeomin and experienced an AE
- Patient received subsequent injections with Xeomin and *did not* experience an AE
- Patient received subsequent injections with Xeomin and experienced an AE
- Patient *discontinued* due to an AE and/or lack of effect and/or secondary non-response
- Patient achieved satisfactory resolution of the condition.

At each injection/Markov cycle, the model included a risk of the following outcomes (see Figure 1): AE, secondary non-response; satisfactory relief from condition; discontinuation due to lack of effect; and other discontinuation.

Salient assumptions were as follows:

- Dysport was a good proxy for the effect of Xeomin in terms of utility changes attributable to treatment.
- Patients could discontinue treatment and, if they did, they returned to their baseline utility value (see Table 1).
- If patients achieved satisfactory relief from their condition, then they attained a utility value of 1.0. (see Table 1).
- The model assumed a linear improvement and decrement in quality of life during a single treatment course.
- This profile assumed an onset of action of eight days [7] and a maximum utility at six weeks post injection [3].
- A utility decrement of 0.02 (assumed) was applied to patients experiencing an AE during an injection cycle.

Figure 1: Structure of the Markov model



This decrement was applied for the full 12-week period of the injection cycle.

- There were no additional costs associated with AEs.

Costs

Only direct healthcare costs were included in the model. Cost of treatment, outpatient visits, administration costs, and hospital costs were included in the structure of the economic evaluation.

As unit doses for individual toxins are product specific and not interchangeable it is common practice to apply a conversion factor to facilitate dose comparisons in clinical practice. The dose ratio between Dysport and Botox has been summarised in the literature between 3:1 and 4:1 according to Odergren et al., Ranoux et al., and Sampaio et al. [12-14]. Wenzel et al. [15] found the ratio to be between 3:1 and 6:1 and Marchetti et al. describes ranges between 2:1 and 11:1 [16]. On the basis of information in the respective SPC's, a dose ratio of 5:1 was used for Dysport:Botox. This was

based on the fact that the recommended initial dose of Dysport in the indication of BP was 120 units per eye [17] and was 25 units for Botox [18]. Use of the conversion rate at a ratio of 5.1 based upon data from the SPC's was validated based on expert clinical opinion.

For the indication of CD, the maximum dose recommended was 1,000 units for Dysport [17] and 200 units for Botox [18]. That is, at a ratio of 5:1, Dysport provided the same level of efficacy and toxicity profile as Botox. The clinical data concluded that Xeomin and Botox provided the same level of efficacy and toxicity in a 1:1 ratio based on the phase III clinical relationships for both indications [6, 11]. These relationships were used to support the use of Dysport and Botox as a proxy for deriving

Table 1: Utility values used in cervical dystonia and blepharospasm economic evaluations

Health status	Cervical dystonia	Blepharospasm	Reference
Baseline utility (at time of first injection)	0.60	0.59	Hilker et al. 2001
Best utility (during first injection cycle)	0.76	0.66	Hilker et al. 2001
Final utility (immediately before next injection)	0.66	0.63	Hilker et al. 2001
Baseline utility (at time of all subsequent injections)	0.66	0.63	Same as final utility. Expert opinion supports the implicit assumption that patients do not revert all the way back to their original baseline quality of life
Best utility (during subsequent injection cycles)	0.76	0.66	Assume same as best utility in initial injection. May be considered conservative given that efficacy does improve over time (Kessler et al. 1999)
Final utility (during all subsequent injections)	0.66	0.63	Assume same as final utility of first injection
Placebo (all cycles)	0.60	0.59	Assume same as baseline value on the basis of expert opinion
Discontinued (all cycles)	0.60	0.59	Assume same as baseline value on the basis of expert opinion
Satisfactory relief (all cycles)	1.00	1.00	Assume back to perfect health

the quality of life, AEs, discontinuation, and cost implications of Xeomin treatment relative to placebo.

Kessler et al. [7] followed 616 patients with CD treated with Dysport for 16 cycles (12-week intervals). Across this study, 3,088 Dysport injections were administered at an average dose of 778 units [7]. This economic evaluation used a Dysport to Xeomin conversion factor of 5:1. Therefore, the average dose of Xeomin used for costing purposes was 155.6 units (778/5). The price of Xeomin was GBP 119.90 for a 100 unit vial. Evidence from the clinical experts, which included Scottish experts, suggests that vials are used across patients to minimise wastage. Therefore, the cost per Xeomin dose in the economic evaluation was GBP 186.56 (155.6 × 119.90/100). The dose conversion from Dysport to Xeomin used for costing purposes was tested in the sensitivity analysis.

The dosing and cost for patients with BP was based on the mean dose per injection observed in the Roggenkämper et al. trial [6]. The average dose of Xeomin used for costing purposes was 40.7 units. Therefore the cost per Xeomin dose in the BP economic evaluation was GBP 48.80 (40.7 × 119.90/100). In sensitivity analyses, the summary of product characteristics dose of 50 units was applied.

Table 2 shows by health state and treatment group the expected utilisation and cost of treatment, visits, and administration in each injection/Markov cycle. This table also shows that the resource utilisation data was largely obtained via expert opinion. However, there are only minimal differences between health states and treatment groups applied in the economic evaluation. Table 3 presents the unit costs applied to these resources.

Utilities

The utility values were elicited using the EuroQol (EQ-5D) [19] at baseline before BoNT/A injections (either Dysport, six patients; or Botox, 44 patients) and at two follow-up visits after 6 weeks and 12 weeks covering one BoNT/A treatment period (see Table 1). The use of the QALY was appropriate for each of the economic evaluations, as the objective of treating CD and BP was to improve a patient's quality of life. In addition, the ICER (GBP/QALY) calculated in the economic evaluation permitted the comparison of the relative cost-effectiveness of Xeomin across different therapeutic areas.

The utility values used in the model were derived from a prospective, open-labelled cohort study of 50 patients with CD (n = 25) and cranial dystonia (n = 25, 20 with BP) reported by Hilker et al. [3].

RESULTS

The incremental cost per QALY gained for Xeomin in the CD indication was GBP 6,441. This result was based on an incremental cost of GBP 2,559 and QALY gains of 0.3973 per patient (see Table 4). In the BP indication, the ICER for Xeomin was GBP 3,734 (see Table 5). This result was based on smaller incremental costs as well as smaller QALY gains relative to the CD indication. The smaller costs were due

Table 2: Resource utilisation applied in the economic evaluation

Resource/Health state	Utilisation per cycle	Total cost	Reference
Xeomin (without adverse events)			
Outpatient visits for Xeomin administration	1.0	£118.00	One for every injection. No other visits necessary on the advice of Scottish experts
Other outpatient visits	0.0	£0.00	One for every injection. No other visits necessary on the advice of Scottish experts
Hospital admissions	0.0	£0.00	Expert opinion/Assumption
Xeomin (with adverse events)			
Outpatient visits for Xeomin administration	1.0	£118.00	The model assumes no additional costs for adverse events on the basis of expert opinion
Other outpatient visits	0.0	£0.00	Expert opinion/Assumption
Hospital admissions	0.0	£0.00	Expert opinion/Assumption
Placebo			
Outpatient visits for Xeomin administration	0.0	£0.00	Not applicable
Other outpatient visits	1.0	£118.00	Expert opinion/Assumption
Hospital admissions	0.0	£0.00	Expert opinion/Assumption
Satisfactory relief			
Outpatient visits for Xeomin administration	0.0	£0.00	Not applicable
Other outpatient visits	0.5	£59.00	Assume half that of placebo
Hospital admissions	0.0	£0.00	Expert opinion/Assumption
Discontinued (failure)			
Outpatient visits for Xeomin administration	0.0	£0.00	Not applicable
Other outpatient visits	1.0	£118.00	Assume same as placebo
Hospital admissions	0.0	£0.00	Expert opinion/Assumption

Table 3: Unit costs applied in the economic evaluation

Resource	Value	Reference
Outpatient visits for Xeomin administration	£118.00	HRG 300F. General Medicine: Face to Face Total Contacts. National Schedule of Reference Costs 2005–06 for NHS Trust and Primary Care Trust Combined. National Schedule of Reference Costs—NHS Trusts and Primary Care Trusts Combined. Outpatient Adult Follow Up Attendance Data. Appendix NSRC4Eiib.
Other outpatient visits	£118.00	HRG 300N. General Medicine: Face to Face Total Contacts. National Schedule of Reference Costs 2005–06 for NHS Trust and Primary Care Trust Combined. National Schedule of Reference Costs—NHS Trusts and Primary Care Trusts Combined. Outpatient Adult Follow Up Attendance Data. Appendix NSRC4Eiib.
Hospital admission	£2,640.99	HRG A11. Muscular Disorders. National Schedule of Reference Costs—NHS Trusts and Primary Care Trusts Combined Non Elective In Patient HRG Data. Appendix NSRC4B.

to a lower Xeomin dose and consequent lower cost. The smaller QALY gains were due to a smaller improvement in utility values from baseline levels in patients with BP.

The cost implications of Xeomin were largely limited to the cost of the Xeomin preparation itself. In a French setting, Brefel-Courbon et al. showed that the net cost of BoNT/A was made up almost entirely of the cost of the treatment itself [20]. Other resources had very little impact on total direct costs. This finding was similar to the results of our study. The main cost difference between the treatment groups (Xeomin and placebo) was that of the Xeomin injections themselves. The same resource utilisation and cost information was used for both the CD and BP economic evaluations.

Table 4: Results of the economic model and the incremental cost-effectiveness of Xeomin in the treatment of cervical dystonia

Treatment group/ Costs	Xeomin	Placebo	Difference
Xeomin	£2,559.42	£0.00	£2,559.42
Administration cost	£1,618.80	£0.00	£1,618.80
Outpatient visits	£168.42	£1,787.77	-£1,619.34
Hospitalisations	£0.00	£0.00	£0.00
Adverse events	£0.00	£0.00	£0.00
Total costs	£4,346.65	£1,787.77	£2,558.88
QALYs	2.5389	2.1417	0.3973
Incremental cost per QALY gained			£6,441.39

Where possible, the design of the sensitivity analysis was consistent for the CD and BP economic evaluations. For both indications, the model was highly sensitive to the difference in the baseline utility and the best utility achieved on treatment. This was not a surprising result given that it was this utility difference that was driving the QALY gains achieved with Xeomin treatment. Nevertheless, even when the utility differences were decreased to 25% of the base case values, the incremental cost per QALY was still less than GBP 30,000 in both indications (GBP 28,635 in CD, GBP 18,606 in BP). In both evaluations, the ICER of Xeomin remained below GBP 20,000 under all plausible Xeomin dose ranges.

Discontinuation rates were not a major driver of cost-effectiveness. This was most likely because a patient that discontinued in the model had reduced costs as well as reduced

benefits. The incidence of AEs was tested over a plausible range (increase and decrease of 50%). AEs had only a small impact on the results of the economic evaluation, with the highest ICER of GBP 6,521 being reached when the incidence of AEs was increased by 50% relative to what was observed for Dysport in Kessler et al. [7].

The average dose, and therefore cost, of Xeomin, was also an important determinant of cost-effectiveness. Nevertheless, Xeomin remained cost-effective under all plausible dose ranges. A sensitivity analysis tested the frequency of Xeomin dosing by administering the dose once every 8 weeks instead of every 12 weeks. With this adjustment the ICER increased to GBP 9,663/QALY. Non-Xeomin resource utilisation had only a very small impact on

Table 5: Results of the economic model and the incremental cost-effectiveness of Xeomin in the treatment of blepharospasm

Treatment group/ Costs	Xeomin	Placebo	Difference
Xeomin	£669.46	£0.00	£669.46
Administration cost	£1,618.80	£0.00	£1,618.80
Outpatient visits	£168.42	£1,787.77	-£1,619.34
Hospitalisations	£0.00	£0.00	£0.00
Adverse events	£0.00	£0.00	£0.00
Total costs	£2,456.69	£1,787.77	£668.92
QALYs	2.2863	2.1071	0.1791
Incremental cost per QALY gained			£3,734.40

cost-effectiveness. In the base case, the additional costs of Xeomin administration were offset by a reduction in the need for outpatient visits. Non-Xeomin resource utilisation increased the ICER only when explicit Xeomin administration costs were included in the model (that is, when the model assumed that Xeomin administration costs would be added to the overall cost profile of treatment, as opposed to being absorbed in the standard management of patients). Even when Xeomin administration costs were included as an incremental cost in the economic evaluation, the ICER remained at the reasonable level of GBP 10,518.

The impact of the variables tested in the sensitivity analysis on the results of the economic evaluation in BP was largely the same as in the CD economic evaluation. Utility values were again an important determinant in the cost-effectiveness of Xeomin. When the effect of Xeomin on utility values was decreased by 75%, the ICER increased from GBP 3,734/QALY gained, which was below the GBP 10,000/QALY threshold.

Importantly, Xeomin administration costs had an important impact on the cost-effectiveness of Xeomin. When administration costs were not offset by outpatient visits in the placebo group, the ICER increased to GBP 12,775/QALY. This large increase was due to the high cost per administration (GBP 118) in the economic evaluation compared to the cost of Xeomin (GBP 48.80 per dose). The cost of AEs was included in the sensitivity analyses. As with the CD economic evaluation, discontinuations and AEs had little impact on the results of the economic evaluation of BP.

Based on discussions with clinical experts there is evidence of active comparators (Dysport and Botox) being used for the indications of BP and CD. A cost utility analysis of Xeomin against active comparators would not be meaningful due to the utilities being the same for all products. When programmes under investigation produce the same outcomes a cost minimisation approach is appropriate [21]. The costs for administration and toxicity are the same between treatments, and cancel each other out, (see Table 6). The difference between costs is driven purely by drug acquisition costs.

The SMC do provide costs of treatment (see Table 7) however, they do state that the doses are for general comparison and do not apply therapeutic equivalence. As previously discussed in the costs section of this paper there

Table 6: Treatment costs excluding drug costs for treating either a blepharospasm or cervical dystonia patient

Treatment group/ Costs	Xeomin	Botox	Dysport
Administration cost	£1,618.80	£1,618.80	£1,618.80
Outpatient visits	£168.42	£168.42	£168.42
Hospitalisations	£0.00	£0.00	£0.00
Adverse events	£0.00	£0.00	£0.00

is variability regarding the dose conversion rates between Dysport and Botox ranging from 3:1 up to 6:1, while the dose ratio between Botox and Xeomin rests at 1:1. If a conservative approach is taken and a dose ratio of 3.5:1 of Dysport to Botox is taken, then for most doses Xeomin has the lowest drug costs out of the BoNT/A treatments, (see Table 8). When a more appropriate dose ratio of 5:1 is applied, based on the SPC conversion rate, Xeomin has the lowest drug costs out of the BoNT/A treatments, (see Table 8) in all cases. It should be noted that in this table the 50 unit vial of Botox is not taken into consideration as the total audited UK IMS data for the 12 months to February 2008 shows there were zero sales of Botox 50 units and only 37 sales of Vistabel 50 unit vials (licensed only for use in aesthetic medicine). This compares to sales of 50,548 vials of Botox 100 units which clearly illustrates this to be the standard presentation used nationwide, and therefore the most valid comparator.

DISCUSSION

This study showed that the incremental cost per QALY gained for Xeomin in the CD indication was GBP 6,441 as compared to placebo. The incremental cost of the Xeomin treatment group was driven almost entirely by the cost of the Xeomin preparation itself. The impact of Xeomin on the

Table 7: Costs of relevant comparators treatment costs excluding drug costs for treating either a blepharospasm or cervical dystonia patient

Drug	Dose regimen for BP	Cost per treatment for BP (£)	Dose regimen for CD	Cost per treatment for CD (£)
Xeomin	No more than 100 units every 12 weeks	120	Usually up to 200 units (maximum 300 units)	up to 240 to 360
Dysport	Usually 60–120 units approximately every 12 weeks	164	250 to 1000 units approximately every 12 weeks	164 to 329
Botox	No more than 100 units every 12 weeks	72–129	Usually up to 200 units	up to 258

Source: In part based on data taken from SMC 2008 [22].

Table 8: Comparison of treatment cost by dose for Xeomin, Botox and Dysport in the UK

		Actual clinical practice cost/ treatment episode			
		Xeomin	Botox	Dysport 3.5:1	Dysport 5:1
Dosage in units for Xeomin/Botox	25	£120	£129	£164	£164
	50	£120	£129	£164	£164
	75	£120	£129	£164	£164
	100	£120	£129	£164	£164
	150	£240	£258	£328	£328
	200	£240	£258	£328	£328
	250	£360	£387	£328	£492
	300	£360	£387	£492	£492
	350	£480	£516	£492	£656
	400	£480	£516	£492	£656
	450	£600	£645	£656	£820
	500	£600	£645	£656	£820

The cost of the 50 unit vial has not been taken into consideration in these costs as UK IMS data showed that there had been zero sales for the 12 months prior to February 2008.

utilisation and cost of other resources estimated in the model was minimal. In the BP indication the incremental cost per QALY gained for Xeomin was GBP 3,734. Similar to the results of the CD economic evaluation, the incremental cost of the Xeomin treatment group was driven almost exclusively by the cost of the Xeomin itself. In both indications, the ICERs were less than GBP 10,000 and indicated that Xeomin was a cost-effective intervention for the treatment of CD and BP. The results demonstrated that Xeomin was highly cost-effective in the management of CD and BP.

For both indications, the model was highly sensitive to the difference in the baseline utility and the best utility achieved on treatment. This was not a surprising result given that it was this utility difference that drove the QALY gains achieved with Xeomin treatment. Nevertheless, even when the utility differences were decreased to 25% of the base case values, the incremental cost per QALY gained was still less than GBP 30,000 in both indications (GBP 28,635) in CD, GBP 18,606 in BP). The average dose, and therefore cost, of Xeomin, was also an important determinant of cost-effectiveness. Xeomin remained cost-effective under all plausible dose ranges.

The impact of the variables tested in the sensitivity analysis on the results of the economic evaluation in CD was

largely the same as in the BP economic evaluation. Importantly, Xeomin administration costs had a significant impact on cost-effectiveness of Xeomin. As with the CD economic evaluation, discontinuations and AEs had little impact on the results of the economic evaluation of BP.

This is the first cost-effectiveness analysis of BoNT/A against placebo in this indication, despite BoNT/A being the *de facto* standard of care. The only reliable costing information in the literature was found in Brefel-Courbon et al. [20]. In this study, these investigators showed that the net cost of BoNT/A was made up almost entirely of the cost of the treatment itself; other resources had very little impact. This was similar to the results of this study. Given this the model is potentially generalisable to many other countries and healthcare systems.

Strengths

A salient strength of this study was its unique nature. To our knowledge there are no other cost-utility studies of BoNT/A in these indications in the literature. This paper is important because it offers the first systematic evaluation of the cost-effectiveness of any BoNT/A in CD and BP. Another strength of this study, which could be also viewed by some as a limitation, is the fact that the comparator was placebo. This is because, heretofore, it has been assumed that BoNT/A was cost-effective in these indications. This means an economic evaluation of Xeomin against the standard of care (being an alternate BoNT/A) would only help to reinforce the *status quo*, despite absence of acceptance that the *status quo* itself represents a cost-effective treatment. For the first time there is evidence supporting the cost-effective use of BoNT/A in CD and BP. It is appreciated that the studies that underpinned this current work may have suffered from small sample size, lack of randomisation, and blinding.

Xeomin is a BoNT/A treatment without complexing proteins. This reduced protein load means that the increased use of Xeomin could result in decreased cumulative protein exposures and consequent neutralising antibody production over time. This is important because CD and BP are not curable and require treatment over extended periods of time. Thus, minimisation of exposure to foreign proteins is an important component of good clinical practice [15].

Of importance for future research is determining which of the BoNT/A treatments is the most cost-effective. The cost minimisation analysis did not take into consideration that Xeomin could be transported without refrigeration and stored at up to room temperature (25°C) for up to four years (unopened vial). Conventional BoNT/A preparations like Botox and Dysport are recommended to be stored

at 2°C–8°C. A gap in the cold chain during transport or storage puts a conventional BoNT/A complex preparation at risk to degenerate or lose potency. These risks are eliminated with Xeomin. The costs of Xeomin are lower than the costs of Botox/Dysport at the dose relativities reported in our study. This suggests that Xeomin is the cost-effective BoNT/A treatment for patients with CD and BP.

The SMC recently reviewed the clinical and economic data for Xeomin in the indications of CD and BP. Based on the evidence, advice was issued stating that “clostridium botulinum neurotoxin type A (Xeomin) is accepted for use within NHS Scotland for the symptomatic management of blepharospasm and cervical dystonia of a predominantly rotational form (spasmodic torticollis) in adults. For both indications, a similar improvement in symptoms has been shown compared to another clostridium botulinum neurotoxin type A” [22]. The SMC review also discussed the results of the cost minimisation model presented to them and concluded that “Xeomin was cheaper for all doses of 75 units and above and for doses below that under certain assumptions” [22]. However, based on all the health economic data presented to them they stated that “Overall the health economic case was considered to have been made” [22].

Limitations

The study has a number of limitations. Firstly, the patient population recruited for the utility study was from a German outpatient movement disorder department, which may limit the generalisability of the results to a UK population [6]. The single most important variables in the cost-effectiveness analyses were the utility values that were collected in a non-randomised, open-label study with relatively small sample sizes [3].

The clinical evidence base of Xeomin is currently not as large as that for other botulinum neurotoxin type A complexes. However, it should be noted that the pivotal trials for Xeomin in these indications under discussion are currently the largest randomised, double-blind studies conducted. Xeomin has since gained an indication for use in upper limb post-stroke spasticity in Argentina, Canada and Mexico. It is also the case that the phase III registration trial is currently the largest trial for the indication of upper limb post-stroke spasticity.

Because complexing proteins predominantly contribute to the bacterial protein content of botulinum toxin, they are thought to increase the risk of antibody formation in general and hence also the risk of the formation of neutralising antibodies against the pure neurotoxin [23]. Xeomin is the first and only botulinum toxin preparation

in which the active substance is free from complexing proteins. Therefore, it carries the lowest clostridial protein load (>8 fold reduction compared to a conventional Botulinum toxin). Because lower protein load is linked with a lower risk for the development of neutralising antibodies, the immunogenic potential of Xeomin is expected to be low and hence may provide a better therapeutic option for patients [23, 24]. By offering a potentially life-long biologic therapeutic with the lowest bacterial protein content Xeomin represents an option which may be particularly attractive in the treatment of new dystonia patients who are expected to require long-term therapy. This low antigenicity even at dose levels clearly exceeding the recommended human dose is a potential main advantage of Xeomin. The immunogenicity benefit has been measured up to 89 weeks [25]. Further long term studies would enable an evaluation of this benefit over differing periods of time. The immunogenicity benefit and that of not requiring cold chain storage for Xeomin are not taken into consideration for the economic evaluation, thereby underestimating the economic benefit of Xeomin.

Another limitation of this study was the indirect comparison between the active products. For example, it was reasoned that Xeomin provided equivalent efficacy and safety to Botox. In addition, the weight of evidence suggested that BoNT/A preparations provided better efficacy, well tolerated and improved quality of life compared to placebo. Therefore, through an indirect comparison, it was reasoned that Xeomin provided better efficacy and improved quality of life compared to placebo.

CONCLUSION

Treatment of CD and BP with Xeomin is a cost-effective intervention with incremental cost per QALY ratios of GBP 6,441 and GBP 3,734 in CD and BP respectively, when compared to placebo. Xeomin shows similar efficacy and toxicity profile to the other botulinum neurotoxins. There are no differences in utility gains, resource utilisation or administration costs between the toxins. In the majority of cases Xeomin represents the BoNT/A treatment with the lowest overall cost for the treatment of CD and BP. In addition to this Xeomin has the added benefits of (i) not requiring cold chain storage and (ii) its potential lower immunogenicity. Xeomin is the only BoNT/A treatment for CD or BP to have advice issued by the SMC accepting it for use within NHS Scotland.

CONFLICT OF INTEREST

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