

clostridium botulinum neurotoxin type A 50, 100, and 200 units powder for solution for injection (Xeomin®)

Merz Pharma UK Ltd

04 October 2019

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

clostridium botulinum neurotoxin type A (Xeomin®) is accepted for use within NHSScotland.

Indication under review: for the symptomatic treatment of chronic sialorrhoea due to neurological disorders in adults.

Clostridium botulinum neurotoxin type A improved unstimulated saliva flow rate and the Global Impression of Change Scale compared with placebo.

Chairman
Scottish Medicines Consortium

Indication

For the symptomatic treatment of chronic sialorrhoea due to neurological disorders in adults.¹

Dosing Information

The optimum dose, frequency and number of injection sites should be determined by the physician on an individual basis. A titration of the dose should be performed. A reconstituted solution at a concentration of 5 units/0.1mL should be used.

Clostridium botulinum neurotoxin type A is injected into the parotid and submandibular glands on both sides (per treatment four injections in total). The dose is divided with a ratio of 3:2 between the parotid and submandibular glands as follows:

Glands	Units	Volume
Parotid glands	30 per side	0.6mL per injection
Submandibular glands	20 per side	0.4mL per injection

The injection site should be close to the centre of the gland. The recommended dose per treatment session is 100 units. This maximum dose should not be exceeded. Treatment intervals should be determined based on the actual clinical need of the individual patient. Repeat treatment more frequent than every 16 weeks is not recommended.

Due to unit differences in the potency assay, unit doses for Xeomin® are not interchangeable with those for other preparations of botulinum toxin type A.

Clostridium botulinum neurotoxin type A may only be administered by physicians with suitable qualifications and the requisite experience in the application of botulinum toxin type A.

Refer to the summary of product characteristics (SPC) for further detail.¹

Product availability date

12 June 2019

Summary of evidence on comparative efficacy

Clostridium botulinum neurotoxin type A blocks cholinergic transmission at the neuromuscular junction preventing neurotransmission. Transmission is eventually re-established by formation of new nerve terminals. This mechanism may affect the nerve impulses which signal saliva secretion from the parotid and submandibular glands.¹

Sialorrhoea in Adults Xeomin Investigation (SIAXI) was a randomised, double-blind, placebo-controlled, international (two countries), multicentre, parallel group study to evaluate the efficacy and safety of clostridium botulinum neurotoxin type A for the treatment of sialorrhoea due to Parkinson's disease, atypical parkinsonism, stroke, or traumatic brain injury.² The study included adult patients with chronic troublesome sialorrhoea continuously for ≥ 3 months prior to screening, as assessed on the Drooling Severity and Frequency Scale (DSFS) sum score (patients required a score ≥ 6 points, range 2 to 9 with higher score indicating greater severity) and modified Radboud Oral Motor Inventory for Parkinson's disease (mROMP).²

Following a screening visit, eligible patients were randomised 2:2:1 to receive treatment with clostridium botulinum neurotoxin type A 100 units or 75 units or equivalent volume placebo every 16 weeks. The main period ran from week 0 to 16 and was followed by an extension period from week 16 to 64, during which patients received clostridium botulinum neurotoxin type A 100 units or 75 units in 3 further cycles of treatment at 16-week intervals.² In each cycle, treatment was administered bilaterally into the parotid and submandibular salivary glands guided by ultrasound or anatomical landmarks. Each treatment consisted of four injections with total doses of active treatment adding up to 100 units or 75 units.²

The SIAXI study had two co-primary outcomes: the change in unstimulated salivary flow rate (uSFR) from study baseline to week 4, and the patient's Global Impression of Change Scale (GICS) score at week 4.² Unstimulated salivary flow rate was assessed by measuring the increased weight of absorbent swabs soaked with produced saliva in the patient's mouth over 5 minutes and then repeating the procedure after 30 minutes, with the average of the 2 flow rates (grams/minute) taken as the result.^{2,3} The patient's and carer's Global Impression of Change Scale score is based on a 7-point Likert scale, ranging from scores of -3 (very much worse) to $+3$ (very much improved) in response to the following question: "Compared to how you were doing just before the last injection into your salivary gland, what is your overall impression of how you are functioning now as a result of this treatment?" If the patient was unable to answer then the carer's impression of the patient score was recorded instead.^{2,3} All patients who received at least one treatment with study medicine and had a baseline value for uSFR were included in the efficacy analyses.²

The analysis of the co-primary outcomes demonstrated a statistically significant advantage for clostridium botulinum neurotoxin type A 100 units over placebo 4 weeks after treatment.² See Table 1 for detailed results.

Table 1. Co-primary outcome results of the SIAXI study at 4 weeks.^{2, 4}

		clostridium botulinum neurotoxin type A 100 units (n=74)	clostridium botulinum neurotoxin type A 75 units (n=74)	placebo (n=36)
Unstimulated salivary flow rate (g/min)	Baseline	0.40	0.42	0.38
	mean change from baseline to 4 weeks	-0.12	-0.07	-0.03
	LS-mean (SE) difference versus placebo	-0.09 (0.031) p=0.004	-0.02 (0.030) p=0.542	-
Patient's Global Impression of Change Scale	mean at 4 weeks ^a	1.04	0.84	0.47
	LS-mean (SE) difference versus placebo	0.58 (0.18) p = 0.002	0.35 (0.18) p = 0.055 ^b	-

LS = least squares, SE = standard error. LS-mean differences may produce results that are slightly different to calculations based on standard means. ^a GICS does not require a baseline measurement. The question includes consideration of baseline. ^b descriptive only as per sequential testing strategy.

The proportion of patients with ≥ 1 point improvement on GICS at week 4 was 73% in the 100 units group compared to 44% of patients in the placebo group.¹ Improvements from baseline in uSFR and GICS were reported for both clostridium botulinum neurotoxin type A doses compared with placebo at weeks 8, 12 and 16. Results for these comparisons were descriptive only.²

Nominal improvements in mean change from baseline in the DSFS sum score (secondary outcome) were reported for both clostridium botulinum neurotoxin type A groups compared with placebo at weeks 4, 8 and 12.²

EuroQol (EQ)-5D-3L visual analogue scale (EQ-VAS) was used to collect data on health-related quality of life but SMC is unable to present the data.

*Other data were also assessed but remain confidential.**

Summary of evidence on comparative safety

Safety analyses were conducted on the safety evaluation set, which included all patients who received clostridium botulinum neurotoxin type A 100 units (n=74), 75 units (n=74) or placebo (n=36) during the main period.² In these groups adverse events (AEs) were reported by 46%, 43%, and 42% of patients; serious AEs were reported by 12%, 8.1%, and 8.3%, treatment related AEs (TAEs) were reported by 8.1%, 9.5%, and 8.3%. No serious TAEs were reported during the main period in any group.²

One patient in both the clostridium botulinum neurotoxin type A 100 units and 75 units groups discontinued the study due to an AE. During the main period the most frequently reported AEs of special interest in the 100 unit group was dry mouth (1.4%) and in the 75 unit group were dysphagia (2.7%), speech disorders (1.4%) and eyelid ptosis (1.4%).²

Life threatening or significant debilitating adverse effects such as dysphagia and pneumonia may result from misplaced injections of clostridium botulinum neurotoxin type A that temporarily paralyse nearby muscle groups. It may only be administered by physicians with suitable qualifications and the requisite experience in the application of botulinum toxin type A.¹

Summary of clinical effectiveness issues

Sialorrhoea may result from excessive saliva production or excessive pooling due to poor swallowing: usually caused by neuromuscular dysfunction (for example, in Parkinson's disease, stroke, traumatic brain injury, motor neurone disease and cerebral palsy), hypersecretion (adverse event of a medicine), or anatomic abnormalities. In patients with atypical parkinsonism it results from decreased swallowing reflexes, causing diminished frequency and efficiency of swallowing of saliva.⁶ Chronic sialorrhoea is associated with perioral dermatitis, facial skin maceration, eating and speaking difficulty, bad breath, sleep disturbance, dehydration and fatigue. Posterior loss of control of saliva is also associated with gagging, choking, coughing, aspiration pneumonia and chest infections. In turn, chronic sialorrhoea has a considerable psychosocial and emotional impact on patients and can have a detrimental effect on the quality of life of both patients and carers.^{2, 6-8}

There are no other licensed medicines for the treatment of sialorrhoea in adults. Non-pharmacological management options include the use of bibs, speech and language therapy and occupational therapy. Off-label anticholinergic therapies, such as oral glycopyrronium bromide, transdermal hyoscine hydrobromide (two most commonly used), sublingual atropine sulphate and ipratropium bromide may be used in some patients but systemic administration is associated with side-effects. Patients with uncontrolled sialorrhoea following treatment with anticholinergic medicines are currently considered for off-label treatment with botulinum neurotoxin type A, usually at a specialist service.^{2, 9-12} Clinical experts consulted by SMC considered that clostridium botulinum neurotoxin type A fills an unmet need in this therapeutic area as there is a lack of licensed treatment options and off-label treatments may not be effective or tolerated.

The SIAXI study demonstrated a statistically significant advantage for clostridium botulinum neurotoxin type A 100 units over placebo, 4 weeks after treatment, for the co-primary outcomes of uSFR and patients' GICS.² The comparison of the 75 unit dose with placebo did not demonstrate a statistically significant difference for the co-primary outcomes. On the GICS a score of +1 is considered a 'minimal improvement': the 100 unit dose of clostridium botulinum neurotoxin type A demonstrated a least squares-mean difference versus placebo of 0.58 at 4 weeks.² This

difference was statistically significant but was less than a 'minimal improvement' and it is uncertain if it is clinically meaningful.

The clinical meaningfulness of the co-primary outcomes is uncertain and did not provide data on important direct health outcomes of sialorrhoea such as perioral dermatitis, dehydration, choking, chest infections and aspiration pneumonia.^{2, 7}

The study excluded patients with motor neurone disease and patients with severe troublesome sialorrhoea, such as those with recurrent aspiration pneumonia and patients with unstable Parkinson's disease. Furthermore, small numbers of patients with atypical parkinsonism, previous stroke, and traumatic brain injury were recruited for the study. Treatment effect in these groups may be uncertain.

There is a lack of comparative data, direct or indirect, comparing clostridium botulinum neurotoxin type A with off-label anticholinergic therapies which are commonly used for this indication.

Clinical experts consulted by SMC considered that the place in therapy of clostridium botulinum neurotoxin type A is to provide a licensed treatment option for patients with chronic sialorrhoea due to neurological disorders. Specialist training is required for administration of a medicine into the salivary glands: this may have service implications.

*Other data were also assessed but remain confidential.**

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis (CUA) comparing clostridium botulinum neurotoxin type A plus standard of care (SoC) to glycopyrronium bromide plus SoC and to SoC alone for the treatment of adult patients with chronic sialorrhoea due to neurological conditions. SoC was stated to include the use of bibs, speech and occupational therapy. SMC clinical experts mentioned there could be some displacement of glycopyrronium bromide, but also potentially transdermal hyoscine hydrobromide patch and sublingual atropine sulphate as first line treatments. A comparison with the latter two treatments was performed as a scenario analysis.

The economic analysis used a Markov model with three severity health states of mild/resolved (DSFS sum score 2 or 3), moderate (DSFS sum score 4 to 6), and severe (DSFS sum score 7 to 9), for patients on-treatment and after discontinuation, plus death. The model used a 16-week model cycle length with half cycle correction applied and adopted a base case time horizon of 10 years. Patients entered the model with moderate (54.6%) or severe (45.4%) sialorrhoea and a mean age of 65 years as per the SIAXI study. It was assumed that once patients had discontinued they would receive only SoC. It was also assumed that for patients receiving SoC only it was not possible to transition to the mild/resolved state.

The clinical data for clostridium botulinum neurotoxin type A plus SoC (100 unit arm) versus SoC alone is taken from the SIAXI study. Transition probabilities for clostridium botulinum neurotoxin type A are based on 16 weeks data from the main part of the study and utilised the 16 to 64 week extension period of the clinical study, and for SoC the transition probabilities were based on the clinical data for the placebo arm which was for 16 weeks only. Extrapolation of the transition probabilities was based on the last observed transition matrix for clostridium botulinum neurotoxin type A and for placebo/SoC. No treatment waning over time for clostridium botulinum neurotoxin type A (or glycopyrronium bromide) was assumed.

As an indirect treatment comparison was stated not to be feasible, the relative effectiveness of glycopyrronium bromide was assumed to be 25% less than clostridium botulinum neurotoxin type A (by assuming 25% lower transition probabilities to better health states). This estimate was based on expert opinion and some evidence on relative improvements in drooling score from NICE clinical guideline 62 in cerebral palsy. On treatment discontinuation, the transition probabilities between health states for SoC were applied. The discontinuation rates for clostridium botulinum neurotoxin type A were derived from the SIAXI study. There was a lack of data for estimation of glycopyrronium bromide discontinuation hence based on clinical expert opinion it was assumed that there would be 50% discontinuation in the first cycle due to the unfavourable AE profile of glycopyrronium bromide, followed by the same discontinuation rate as for clostridium botulinum neurotoxin type A from cycle 2 onwards.

Mortality in the economic analysis was based on Scottish life tables with a standardised mortality ratio (SMR) of 4.07 applied based on a weighted average for Parkinson's and stroke patients in the SIAXI study.

The health state utilities used in the base case were derived from the NICE clinical guideline 62 in children and young people under 25 years with cerebral palsy, which reported utilities according to DSFS category, estimated at 0.5346, 0.4283 and 0.3008 for mild/resolved, moderate and severe sialorrhoea respectively. The EQ-5D-3L was included in the SIAXI study with regression analysis of this data producing estimated utilities of 0.6397, 0.5974, and 0.5854 for mild/resolved, moderate and severe sialorrhoea states respectively. These utilities were applied in scenario analysis. Due to the favourable safety profile of clostridium botulinum neurotoxin type A adverse events were not included in the economic analysis, so no AE disutilities or costs were applied.

Costs included medicine acquisition costs, administration costs and health state resource use costs. This was based on 100 unit injections for clostridium botulinum neurotoxin type A per 16 week cycle, with glycopyrronium bromide administered orally as tablets (59% of patients) or solution (41% of patients). Administration of clostridium botulinum neurotoxin type A was costed on the basis of a consultant outpatient appointment and the use of ultrasound scanning in a proportion of patients. No additional service set up or training costs were included. No direct cost was assumed for SoC (as it was used in all treatment arms). Resource use by health state consisted of use of speech therapy and occupational therapy visits estimated based on expert opinion.

The base case results for clostridium botulinum neurotoxin type A plus SoC versus glycopyrronium bromide plus SoC, and versus SoC alone for the patients with chronic sialorrhoea are presented in Table 2 below. Clostridium botulinum neurotoxin type A plus SoC is estimated to dominate glycopyrronium bromide plus SoC, with cost savings and quality adjusted life year (QALY) gains of 0.17 estimated. The main driver of the cost savings were the lower medicine costs estimated for clostridium botulinum neurotoxin type A. For the comparison with SoC the estimated incremental cost-effectiveness ratio (ICER) was £10,327/QALY, with incremental costs of £3,101 and QALY gains estimated at 0.30. QALY gains were driven by a larger proportion of patients transitioning to better health states than the comparators, in particular to the mild/resolved state.

Table 2: Base case results Clostridium botulinum neurotoxin type A plus SoC vs glycopyrronium bromide plus SoC, and vs SoC alone

Comparator	Incremental costs	Incremental QALYs	ICER (Cost/QALY)
Glycopyrronium bromide plus SoC	-£7,727	0.17	Clostridium botulinum neurotoxin type A plus SoC dominant
SoC	£3,101	0.30	£10,327

ICER=incremental cost-effectiveness ratio, QALY=quality adjusted life year, SoC=standard of care

Sensitivity analysis presented in the submission demonstrated sensitivity to the estimated treatment discontinuation rates for each treatment from cycle 2 onwards (for the comparison with glycopyrronium bromide), the utility estimate for the mild/resolved health state, and the starting age of patients. Results from key scenario analyses are presented in Tables 3 and 4 below.

A scenario analysis using EQ-5D derived utilities from the SIAXI study resulted in an estimated ICER versus SoC of £36,215/QALY, and reduced QALYs gained for the comparison with glycopyrronium bromide although clostridium botulinum neurotoxin type A was still estimated to be dominant. There were still cost savings but much lower QALYs gained for a scenario assuming equal efficacy for glycopyrronium bromide and clostridium botulinum neurotoxin type A (Table 3 below). Scenario analysis around the discontinuation rate showed the only scenario to result in an incremental cost and ICER estimate for clostridium botulinum neurotoxin type A versus glycopyrronium bromide was if the discontinuation rate for the latter was set at 75% for all cycles (Table 3).

Scenario analysis comparing clostridium botulinum neurotoxin type A with transdermal hyoscine hydrobromide and atropine sulfate and assuming the same efficacy and discontinuation rate as glycopyrronium bromide resulted in ICERs of £10,318 and £15,552/QALY respectively. The ICERs were driven by the lower acquisition costs for these medicines compared to glycopyrronium bromide. There was relatively low sensitivity to varying the time horizon, baseline health state distributions, application of stopping rules, resource use/cost estimates, or setting the SMR at one.

Table 3: Selected scenario analysis results (clostridium botulinum neurotoxin type A versus glycopyrronium bromide)

	Scenario analysis	Incremental cost	Incremental QALY	ICER (Cost/QALY)
1	Equal efficacy with glycopyrronium bromide	-£7,663	0.15	clostridium botulinum neurotoxin type A dominant
2	Discontinuation rate of 75% for glycopyrronium bromide (all cycles)	£976	0.30	£3,308
3	Discontinuation rate of 75% for glycopyrronium bromide in cycle 1 only	-£3,118	0.24	clostridium botulinum neurotoxin type A dominant
4	Using EQ-5D utilities	-£7,727	0.05	clostridium botulinum neurotoxin type A dominant
5a	Alternative comparator: transdermal hyoscine hydrobromide	£1,766	0.17	£10,318
5b	Alternative comparator: transdermal hyoscine hydrobromide (EQ-5D utilities)	£1,766	0.05	£36,338
6a	Alternative comparator: atropine sulfate	£2,662	0.17	£15,552
6b	Alternative comparator: atropine sulfate (EQ-5D utilities)	£2,662	0.05	£54,770

ICER=incremental cost-effectiveness ratio, QALY=quality adjusted life year

Table 4: Selected scenario analysis results (clostridium botulinum neurotoxin type A versus SoC)

	Scenario analysis	Incremental cost	Incremental QALY	ICER (cost/QALY)
1	Using EQ-5D utilities	£3,101	0.09	£36,215
2	Transition probabilities based on average DSFS improvement over 4 cycles	£3,224	0.26	£12,528
3	Treatment waning at year 3 (apply SoC transition probabilities)	£3,113	0.30	£10,539
4	10% of SoC patients transition to mild after cycle 1	£3,186	0.27	£11,742

ICER=incremental cost-effectiveness ratio, QALY=quality adjusted life year, SoC=standard of care

There were a number of issues in the economic analysis:

- A lack of evidence of relative effectiveness versus glycopyrronium bromide meant the estimation of benefit for clostridium botulinum neurotoxin type A over this comparator used in the economic analysis is highly uncertain. The results were also sensitive to applying the EQ-5D utilities which resulted in reduced QALY gains, but still cost savings (Table 3 scenario 4). The company has provided a scenario analysis in which equal effectiveness with glycopyrronium

bromide is assumed with cost savings still estimated due to the relatively high acquisition cost of glycopyrronium bromide (Table 3 scenario 1).

- There is high uncertainty over the discontinuation rates assumed for glycopyrronium bromide, set at an arbitrary 50% in the first cycle due to AEs. This has been tested in a range of scenario and sensitivity analysis with clostridium botulinum neurotoxin type A remaining cost saving under most scenarios (Table 3 scenarios 2 and 3).
- Based on SMC expert opinion, it is expected that many patients would be offered clostridium botulinum neurotoxin type A when there is an inadequate response to anticholinergics or these are considered unsuitable, hence SoC alone is an important comparator. There were some limitations with the data inputs for analysis and some concerns that the relative long-term outcomes for clostridium botulinum neurotoxin type A versus SoC may be overestimated given the way the transition probabilities were calculated and an assumption of no treatment waning effects being used. However, the company provided additional scenario analyses using transition probabilities based on average DSFS score over all 4 cycles for clostridium botulinum neurotoxin type A, and allowing treatment waning in order to test these uncertainties, with limited impact on the ICER (Table 4).
- There is uncertainty over the health state utility estimates used in the economic analyses, and corresponding uncertainty over the health related quality of life impact of sialorrhoea and benefit of clostridium botulinum neurotoxin type A. The base case values may not be generalisable to the adult patient population to be treated with clostridium botulinum neurotoxin type A. In contrast the clinical study- derived EQ-5D utilities may be pessimistic. The results are sensitive to the use of EQ-5D utilities, in particular for the comparison with SoC (with an upward impact on the ICER to over £36,000/QALY). The company provided a useful threshold analysis that indicated that a utility difference of 0.08 between mild and severe states would be associated with an ICER below £30,000/QALY.
- SMC clinical experts have indicated that hyoscine hydrobromide and atropine sulfate could be relevant comparators – these comparators were included in a rudimentary scenario analysis and, due to the much lower acquisition cost than glycopyrronium bromide, are associated with an ICER rather than cost savings (Table 3). The ICERs were within acceptable bounds although upwardly sensitive to a scenario applying the EQ-5D utilities (Table 3).

Despite these limitations, the economic case was considered demonstrated.

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from: Ataxia UK, the Neurological Alliance of Scotland, Parkinson's UK Scotland and MND Scotland. Ataxia UK, Parkinson's UK Scotland and MND Scotland are all registered charities. The Neurological Alliance of Scotland is a Scottish Charitable Incorporated Organisation (SCIO).

- Ataxia UK, the Neurological Alliance of Scotland and MND Scotland have not received any pharmaceutical company funding in the past two years. Parkinson's UK Scotland has received less than 0.04% pharmaceutical company funding in the past two years, with none from the submitting company.
- Sialorrhoea can cause: choking, skin problems, infections, distress and embarrassment for people with neurological conditions including motor neuron disease (MND), Parkinson's, multiple sclerosis, Huntington's, stroke, cerebral palsy and ataxia. It can make it difficult to be understood when speaking; it can make eating and drinking harder; and it can cause people to withdraw from social activities and even employment, triggering social isolation and financial hardship. Unmanaged drooling also has a very significant impact on unpaid carers, causing emotional distress, social isolation, and increased domestic tasks.
- Sialorrhoea is often untreated, as existing treatment options are not clinically appropriate for some people with neurological disorders. The medicines which are available may cause side effects such as dry mouth and skin irritation and they may make common cognitive and neuropsychiatric symptoms worse in patients with Parkinson's. Sialorrhoea is often managed using practical aids (such as bibs) and interventions from speech and language therapists. However many people with neurological conditions find it difficult to access speech therapy to aid with saliva and swallowing.
- If effective, the new medicine could reduce choking and infections; increase self-confidence; improve speech; and improve quality of life for patients with neurological disease and their families.
- The patient groups highlighted that accessing clostridium botulinum neurotoxin type A will be difficult for some people with complex conditions who find it difficult to travel to clinics for administration of treatment.

Additional information: guidelines and protocols

The indication being considered in this submission is the management of chronic sialorrhoea associated with neurological conditions. Because there is no single source of guidance covering this condition, UK guidance on cerebrovascular accident, motor neurone disease, Parkinson's disease, and palliative care was reviewed. Relevant guidance and recommendations identified are outlined below and are broadly consistent across the different guidelines.

The Scottish palliative care guidelines were originally published in 2014 and were subsequently updated in 2019.⁹ This guidance includes recommendations on symptom control and mouth care that make relevant recommendations for the management of sialorrhoea. The guidance recommends the off label use of glycopyrronium bromide, hyoscine hydrobromide, amitriptyline, and atropine and recommends that glycopyrronium should be used as first-line treatment in

patients who have cognitive impairment, because it has fewer central nervous system side effects.⁹

The National Institute for Health and Care Excellence (NICE) published Motor neurone disease: assessment and management: NICE guideline 42 in 2010 and the guidance was subsequently updated in 2019.¹² This guideline recommends that an antimuscarinic medicine should be considered as the first line treatment for sialorrhoea in patients with motor neurone disease. In patients who have cognitive impairment the use of glycopyrronium bromide should be considered as the first line treatment because it has fewer central nervous system adverse events. If the first line treatment of sialorrhoea is ineffective, not tolerated, or contraindicated consideration should be given to referral to a specialist service for botulinum toxin A.¹²

NICE published Parkinson’s disease in adults: NICE guideline 71 in 2006, the guideline was subsequently updated in 2017,¹⁰ and Cerebral palsy in under 25s: assessment and management: NICE guideline 62 in 2017.¹¹ Both made similar recommendations to NICE guideline 42 for the management of sialorrhoea.

Additional information: comparators

Off-label oral glycopyrronium bromide, transdermal hyoscine hydrobromide, atropine drops, ipratropium spray.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
clostridium botulinum neurotoxin type A	100units injected into the parotid and submandibular glands every 16 weeks	422
glycopyrronium bromide (off-label)	1mg oral once daily up to 2mg oral three times daily Tablets Solution	2,190 to 7,207 1,107 to 6,625
atropine (off-label)	1 to 4 (1%) drops sublingual daily	1,714 ^A
hyoscine hydrobromide (off-label)	1.5mg patches, changed every 72 hours	781
ipratropium bromide (off-label)	2 (21microgram/dose) sprays sublingually once daily	27

Doses are for general comparison and do not imply therapeutic equivalence. Costs from BNF/BNFc online on 06 August 2019. ^A calculation accounted for discarding each bottle 28 days after opening.

Additional information: budget impact

The submitting company estimates that the total number of patients eligible for treatment would be 5,504 in year 1, rising to 8,318 in year 5 based on prevalent patients in year one and around 700 newly diagnosed patients each year 2-5. Based on estimates of 35% uptake in year 1 for clostridium botulinum neurotoxin type A, rising to 90% in year 5, and a discontinuation rate between 8.84% and 10.03% in each of the five years, the estimated number of patients treated with clostridium botulinum neurotoxin type A in year 1 was 1,756, rising to 2,842 patients in year 5.

The gross additional medicines cost has been estimated to be £1.8m for year 1 up to £2.8m in year 5, and after displacement of comparator medicines a net saving of £239k was estimated for year 1 increasing to a saving of £387k in year 5.

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This assessment is based on data submitted by the applicant company up to and including 13 September 2019.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are

therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.