

National Institute for Health and Care Excellence

Single Technology Appraisal (STA)



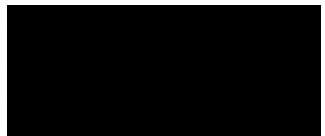
Clostridium botulinum neurotoxin type A for treating chronic sialorrhoea in adults

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Association of British Neurologists	Yes – I agree this is an appropriate topic for NICE . It is a common problem but in my clinical experience 50% of those with neurological conditions experiencing sialorrhoea seems an overestimate.	Comments noted. The background section on the prevalence of sialorrhoea has been amended accordingly in the scope.
	Merz Pharma	Yes, this topic is appropriate for referral; sialorrhoea (hypersalivation) is a common condition in patients who suffer from neurological conditions, adding to the negative impact that these conditions can have on quality of life. It can also arise as a result of infections (e.g. tonsillitis, mumps), problems with the jaw such a fracture or dislocation, radiation therapy, and result of drug use (drug-induced sialorrhoea).	Comments noted.

Section	Consultee/ Commentator	Comments [sic]	Action
			
	University College London Hospital NHS Foundation Trust – National Hospital for Neurology and Neurosurgery	Yes. There is currently a lack of specific guidance regarding this issue.	Comment noted.
Wording	Association of British Neurologists	No. The references for prevalence of Hypersalivation both appear to be for cerebral palsy. The estimated numbers for Parkinson's appear rather high, the prevalence is often estimated at 127,000 total, so approx 50% of that number would be more accurate.	Comments noted. The estimated numbers for Parkinson's disease have been amended accordingly in the scope.
	Merz Pharma	The wording of the remit is broadly appropriate. 	Comment noted. 

Section	Consultee/ Commentator	Comments [sic]	Action
			[REDACTED]
	University College London Hospital NHS Foundation Trust – National Hospital for Neurology and Neurosurgery	No comment	Noted.
Timing Issues	Association of British Neurologists	We would not rate this as urgent. Whilst it is a common problem, that affects many, this is another option for symptomatic treatment, not curative treatment. There are already a number of widely available other treatments that are effective in significant numbers of people with neurological conditions and sialorrhoea. In my experience botulinum toxin is already being used, off licence, in some refractory cases.	Comment noted.
	Merz Pharma	Although some treatment options are available, there remains an unmet need for effective treatments that can reduce the severity and frequency of hypersalivation in patients and consequently improve patient quality of life in adults suffering from sialorrhoea associated with neurological conditions.	Comment noted.
	University College London Hospital NHS Foundation Trust – National Hospital for	Not urgent.	Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
	Neurology and Neurosurgery		
Additional comments on the draft remit	Association of British Neurologists	None	Comment noted.
	Merz Pharma	None	Comment noted.
	University College London Hospital NHS Foundation Trust – National Hospital for Neurology and Neurosurgery	None	Comment noted.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Association of British Neurologists	In our experience 50% of those with neurological conditions experiencing sialorrhoea seems an overestimate. We note that the reference refers to people who have ALS/MND, who often have significant bulbar problems, rather than a more general neurological population.	Comments noted. The background section on the prevalence of sialorrhoea has been amended accordingly in the scope.

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	Merz Pharma	<p>Although the draft scope provides an accurate summary of the association of sialorrhoea with neurological conditions, the background wording does not communicate the impacts of the condition on patients' quality of life. The population at large are likely to underappreciate the impact that hypersalivation can have and therefore we believe it is important that the negative impacts of the condition are highlighted briefly as part of the background information. Such negative impacts can include:</p> <ul style="list-style-type: none"> • Difficulty swallowing, eating and speaking • Dehydration • Reduced oral hygiene • Increased risk of respiratory tract infections • Social embarrassment and isolation • Depression and anxiety (on the part of the patient and the caregiver) 	Comments noted. The background section has been amended to include some of the negative impacts of sialorrhoea.
	University College London Hospital NHS Foundation Trust – National Hospital for Neurology and Neurosurgery	Accurate information. However, an additional cause of hypersalivation may be 'reduced frequency of swallowing'. This could be due to initiation (such as in PD), reduced sensation to build up of oral/pharyngeal secretions or reduced level of consciousness.	Comments noted. The background section is only intended to provide a brief overview of the potential causes of sialorrhoea. No changes to the scope are therefore needed.
The technology/ intervention	Association of British Neurologists	Yes	Comment noted. No changes to the scope are needed.

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	Merz Pharma	Yes, the description of the technology is accurate	Comment noted. No changes to the scope are needed.
	University College London Hospital NHS Foundation Trust – National Hospital for Neurology and Neurosurgery	No comment	Noted.
Population	Association of British Neurologists	<i>Is the population defined appropriately? Yes</i> <i>Are there groups within this population that should be considered separately?</i> No. Motor neurone disease is not mentioned.	Comment noted. Scoping workshop attendees agreed to widen the definition of the population in the scope. This now includes adults with chronic sialorrhoea.
	Merz Pharma	The population should be reworded as adults with chronic sialorrhoea. [REDACTED]	Comment noted. Scoping workshop attendees agreed to widen the definition of the population in the scope. This now

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			includes adults with chronic sialorrhoea.
	University College London Hospital NHS Foundation Trust – National Hospital for Neurology and Neurosurgery	<p>Hypersalivation is frequently a distressing and embarrassing symptom of Motor Neurone Disease. The Motor Neurone Disease Association provides useful guidance on this. Patients who are ‘nil by mouth’ may present with additional challenges with relation to oral care and hygiene. Dry mouth makes this worse so challenging saliva management needs to be balanced with xeristoma.</p> <p>Patients who already have dysphagia would be at increased risk of worsened dysphagia.</p>	<p>Comments noted. Scoping workshop attendees agreed to widen the definition of the population in the scope. This now includes adults with chronic sialorrhoea.</p> <p>In addition, it was agreed to include patients with swallowing difficulties (dysphagia) as a subgroup in the scope.</p>
Comparators	Association of British Neurologists	<p><i>(Is this (are these) the standard treatment(s) currently used in the NHS with which the technology should be compared? Can this (one of these) be described as ‘best alternative care’)</i> Yes. In addition, atropine 1% eye drops used orally and tricyclic antidepressants such as amitriptyline are also used in the adult population.</p>	<p>Comment noted. Atropine 1% eye drops and tricyclic antidepressants are not included as comparators because they are not considered established practice in the NHS for treating sialorrhoea.</p>

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	Merz Pharma	<p>Based on our current understanding, the comparators listed in the draft scope appear appropriate. However, we are currently still determining the treatment(s) that comprise standard of care in practice and cannot comment definitively on a final list of comparators at the current time.</p> <p>Oral glycopyrronium bromide certainly represents a comparator and likely represents the best alternative care in clinical practice. This is consistent with its recommendation as the treatment for managing drooling of saliva in the NICE guidelines for Parkinson's disease in adults and for cerebral palsy in under 25s, as well as the availability of NICE evidence summaries on this therapy. It is also currently the only licensed therapy in this indication. Hyoscine hydrobromide may also be used in some cases in clinical practice, but their use is unlicensed in this indication.</p>	Comment noted. Scoping workshop attendees agreed that the most appropriate comparators are anticholinergics.
	University College London Hospital NHS Foundation Trust – National Hospital for Neurology and Neurosurgery	Yes, but Atropine is also used in addition (1 drop sublingually). This can be effective in some patients and provides an option as a PRN medication (so, using on bad days, or if going out of the house). These medications are also sometimes used in combination to a greater effect. In addition, in my experience (and anecdotally), it may be that one medication will work for a time, and then become less effective, resulting in the need for a rotation of different medications. I am also aware of research in to Botox Type B in PD and ALS which have shown significant benefits and suggest it to be a safe treatment (Jackson et al 2009, Hunter et al 2004), with lower risk of dysphagia.	Comment noted. Atropine 1% eye drops, tricyclic antidepressants and Botox Type B are not included as comparators because they are not considered established practice in the NHS for treating sialorrhoea.
Outcomes	Association of British Neurologists	Yes	Comment noted. No changes to the scope are needed.
	Merz Pharma	The outcomes specified capture important health-related benefits of Xeomin in this indication.	Comments noted. No changes to the scope

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		<p>It should be noted that the Global Impression of Change Scale is an important outcome measured in the trials of Xeomin. This outcome measures the impression of treatment efficacy and impact on the patient from the perspective of the patient or carer and hence provides an important measure of the meaningfulness of treatment benefit.</p> <p>An important outcome that is currently absent from the draft scope is that of caregiver burden. Burden on caregivers represents an important aspect of the condition and this impact should be considered as part of the appraisal.</p>	<p>required. The outcomes section is intended to include the main outcome measures of interest and therefore does not specify any particular measurement scales. Global Impression of Change Scale would likely be captured in the 'response rate' outcome that is specified in the scope.</p> <p>The scope aims to identify principal measures of health outcome(s) that will be relevant for the estimation of clinical effectiveness. That is, they measure health benefits and adverse effects that are important to patients and/or their carers. Burden on caregivers could be accounted for in the outcomes of "response rate" and</p>

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			<p>“health-related quality of life” In addition to evidence on treatment effects and costs, the appraisal requires consideration of organisational issues that affect patients, carers and healthcare providers.</p>
	<p>University College London Hospital NHS Foundation Trust – National Hospital for Neurology and Neurosurgery</p>	<p>The Drooling Impact Scale (Reid et al 2009) is a nice scale for measuring the daily impact of drooling on quality of life, but this is only validated for use in children. A measure or subjective questionnaire that gains the opinions of patients/carers on the impact of hypersalivation would be beneficial. Or, a Visual Analogue Scale (VAS) of patient and carer assessment of saliva problem, such as used in Jackson et al 2009 (Randomized double-blind study of botulinum toxin type B for sialorrhoea in als patients). ‘Number of tissues used in a day’ may also be a useful measure.</p> <p>A dysphagia outcome measure such as EAT-10 or Therapy Outcome Measures or a VAS may be useful to measure dysphagia side effects.</p>	<p>Comments noted. The outcomes section is only intended to include the main outcome measures of interest and therefore does not specify any particular measurement scales. No changes to the scope are therefore needed.</p>
Economic analysis	Association of British Neurologists	No comment	Noted.
	Merz Pharma	<p>At this point, we are unable to recommend the most appropriate time horizon for the economic analysis, However, a lifetime time horizon is likely to be inappropriate as treatment for sialorrhoea does not impact on mortality and treatment is not expected to be life-long. A long time horizon would introduce</p>	<p>Comment noted. The reference case stipulates that the time</p>

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		requirements for extrapolation of data, which would create unnecessary uncertainty in the economic analysis.	horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. No changes to the scope are needed.
	University College London Hospital NHS Foundation Trust – National Hospital for Neurology and Neurosurgery	No comment	Noted.
Equality and Diversity	Association of British Neurologists	No equality and diversity issues	Comment noted.
	Merz Pharma	We are not aware of any equality issues.	Comment noted.
	University College London Hospital NHS	No comment	Noted.

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	Foundation Trust – National Hospital for Neurology and Neurosurgery		
Other considerations	Association of British Neurologists	nil	Comment noted.
	Merz Pharma	N/A	Noted.
	University College London Hospital NHS Foundation Trust – National Hospital for Neurology and Neurosurgery	Hypersalivation needs to be distinguished from other kinds of difficult secretion management (such as thick, stringy secretions which may be more difficult for patients to manage with increased dryness). This can be particularly challenging when both are experienced at the same time.	Comment noted. Scoping workshop attendees agreed to include patients with swallowing difficulties (dysphagia) as a subgroup in the scope.
Innovation	Association of British Neurologists	Neurorehabilitation Advisory group: no It is a treatment that is already available. To me it is simply another option for those who have not gained sufficient symptomatic relief from non-pharmacological and other pharmacological measures nit a step change I cannot think of any health benefits unlikely to be included in the QALY	Comment noted. The committee will consider the innovative nature of the technology at the time of the appraisal. No changes to the scope are needed.

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		<p>Movement Disorders Advisory group: It is innovative in targeting a local problem with a local treatment, so avoiding systemic side effects, in particular cognitive problems which are very relevant in the target populations.</p>	
	Merz Pharma	<p>Patients suffering from sialorrhoea as a result of neurological conditions are already faced with the physical, emotional and/or social burdens imposed by their neurological condition. Sialorrhoea in patients with neurological conditions therefore serves to impose an additional burden on patients who are already subject to notable detrimental impact on their quality of life.</p> <p>Sialorrhoea has been associated with negative impacts on a number of aspects of patients' quality of life, including physical sequelae such as poor oral hygiene, dehydration, difficulties eating and speaking and risk of respiratory tract infections, as well as psychosocial impacts such as emotional distress and social embarrassment. Current pharmacological treatments for sialorrhoea are of limited effectiveness and there is therefore an unmet need for effective treatments to improve quality of life for patients with chronic sialorrhoea.</p> <p>Xeomin provides an innovation in this regard:</p> <ul style="list-style-type: none"> • It is likely to provide a higher efficacy treatment option and hence improved quality of life • Compared to oral glycopyrronium bromide, which requires frequent (multiple daily) administration of oral solution, botulinum toxin would represent a step-change in the management of the condition by providing a treatment option that requires infrequent intervention to achieve control of drooling. This may help to improve adherence rates versus these more frequently administered treatments. 	<p>Comment noted. The committee will consider the innovative nature of the technology at the time of the appraisal. No changes to the scope are needed.</p>

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		<ul style="list-style-type: none"> Treatment of sialorrhoea can often provide as great or greater benefit to family members/caregivers as the patient. Xeomin therefore has the potential to relieve the considerable burden of caring for chronic sialorrhoea patients that is placed on family members or caregivers. 	
	University College London Hospital NHS Foundation Trust – National Hospital for Neurology and Neurosurgery	Yes	Comment noted. The committee will consider the innovative nature of the technology at the time of the appraisal. No changes to the scope are needed.
Questions for consultation	Association of British Neurologists	No comments	Comment noted.
	Merz Pharma	<ul style="list-style-type: none"> Oral glycopyrronium bromide represents established clinical practice in the NHS. This is consistent with its recommendation as the treatment for managing drooling of saliva in the NICE guidelines for Parkinson’s disease in adults and for cerebral palsy in under 25s, as well as the availability of NICE evidence summaries on this therapy. It is also currently the only licensed therapy in this indication. Hyoscine hydrobromide may also be used in some cases in clinical practice, but their use is unlicensed in this indication. Surgery or radiotherapy would not be considered for the symptomatic treatment of chronic sialorrhoea as a comparator to Xeomin. Guidelines refer to “pharmacological management” of the condition, which does not include surgery or radiotherapy. 	Comments noted. No changes to the scope are needed.

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		<ul style="list-style-type: none"> • The outcomes listed are appropriate. The list should be updated to include patient/carer/investigator perception of treatment efficacy (measured by the Global Impression of Change Scale). In addition, caregiver burden should be included as an outcome as it is an important aspect of the condition. • Drug-induced vs neurologic condition, different types of neurologic conditions • We consider that Xeomin in the planned indication would fit into the following places within the “Neurological conditions” NICE pathway (reflecting the fact that chronic sialorrhoea is prevalent in a number of neurologic conditions and the patients in which there is evidence for efficacy and safety of Xeomin): <ul style="list-style-type: none"> ○ Parkinson’s disease ○ Atypical parkinsonism (multiple system atrophy, corticobasal degeneration or progressive supranuclear palsy) ○ Cerebral palsy ○ Post-stroke ○ Traumatic brain injury 	
	University College London Hospital NHS Foundation Trust – National Hospital for Neurology and Neurosurgery	No comments	Comment noted.

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Additional comments on the draft scope	Association of British Neurologists	Many of these patients may have cognitive changes as part of their neurological condition and lack capacity to consent to botulinum toxin injections. In this group, we would need to apply the Mental Capacity Act and used Best Interests decision making unless they have a Lasting Power of Attorney or a Court of Protection appointed Deputy for Health and Welfare.	Comments noted. No changes to the scope are needed.
	Merz Pharma	None	Noted.
	University College London Hospital NHS Foundation Trust – National Hospital for Neurology and Neurosurgery	None	Noted.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health and Social Care
UK Multiple Sclerosis Specialist Nurse Association

National Institute for Health and Care Excellence