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# HEALTH TECHNOLOGY BRIEFING
# JULY 2020

# Xeomin for sialorrhea in children and adolescents aged 2 to 17 years

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| **NIHRIO ID** | 24185 | **NICE ID** | 10097 |
| **Developer/Company** | Merz Pharma | **UKPS ID** | 647682 |

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| **Licensing and market availability plans** | Currently in phase III clinical trials. |

## SUMMARY


Xeomin is in clinical development for the treatment of chronic sialorrhea associated with neurological disorders and/or intellectual disability in children and adolescents aged 2 to 17 years. Sialorrhea is excess saliva accumulation, usually due to problems swallowing, leading to drooling. Sialorrhea can lead to complications including skin infections and breathing problems, but also embarrassment and social isolation.

Xeomin is one formulation of botulinum neurotoxin type A. It is injected into salivary glands and reduces saliva production. Currently, it is recommended as a specialist option for treating sialorrhea in children and adolescents, but is not yet licensed for this indication. It is an alternative to anticholinergic drugs which are also used to reduce saliva flow, but which can have side effects in a number of patients. If licensed, Xeomin will offer an additional treatment option for chronic sialorrhea in children and adolescents aged 2 to 17 years.

# PROPOSED INDICATION

Treatment of children and adolescents aged 2 to 17 years with chronic sialorrhea associated with neurological disorders and/or intellectual disability.[1,a]

# TECHNOLOGY

## DESCRIPTION

Xeomin is a clostridium botulinum neurotoxin type A, free from complexing proteins (IncobotulinumtoxinA, NT 201); it blocks cholinergic transmission at the neuromuscular junction by inhibiting the release of acetylcholine. The nerve terminals of the neuromuscular junction no longer respond to nerve impulses, and secretion of the neurotransmitter at the motor endplates is prevented (chemical denervation). Recovery of impulse transmission is re-established by the formation of new nerve terminals and reconnection with the motor endplates.[2]

Xeomin is one of three botulinum toxin A products licensed in the UK – the other two being onabotulinumtoxinA (Botox) and abobotulinumtoxinA (Dysport). They are not all licensed for the same indications. Due to differences in manufacturing processes, formulations, and the assay methods used to determine units of biological activity, these products are not interchangeable.[3]

Xeomin is in clinical development for the treatment of chronic sialorrhea associated with neurological disorders and/or intellectual disability in children and adolescents. In the phase III clinical trial (SIPEXI, NCT02270736), patients received on average 2 units Xeomin per kilogram body weight per treatment cycle (subjects with a body weight ≥ 30kg to receive a fixed total dose of 75 units per cycle).[1]

## INNOVATION AND/OR ADVANTAGES

Currently, the main medications used to treat sialorrhea are anticholinergic drugs.[4] Anticholinergic drugs are not always effective and can have a number of significant side effects that can prompt cessation of treatment.[5] Furthermore, due to lack of long-term safety data, glycopyrronium bromide is only recommended for short term use and total treatment duration should be kept as short as possible.[6]

If anticholinergic drugs provide insufficient benefit or are not tolerated to reduce the severity and frequency of drooling in children and young people with cerebral palsy, NICE currently recommend considering off-label use of botulinum toxin A injections to the salivary glands. Xeomin is the only preparation of botulinum toxin A to have a marketing authorisation and recommendation by NICE for treating chronic sialorrhea caused by neurological conditions in adults, and no botulinum toxin A products are currently licensed for sialorrhea in patients aged under 18.[7,8]

## DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Xeomin is currently indicated in adults for the symptomatic treatment of:[2]

- blepharospasm and hemifacial spasm
- cervical dystonia of a predominantly rotational form (spasmodic torticollis)
- spasticity of the upper limb

[a] Information provided by Merz Pharma on UK PharmaScan

- chronic sialorrhea due to neurological disorders

Very common adverse effects associated with Xeomin include: eyelid ptosis (when used to treat blepharospasm and hemifacial spasm) and dysphagia (when used to treat spasmodic torticollis).

It is currently in phase III development for several indications including spasticity of the lower limb in adults, and limb spasticity in children and adolescents.[9-11]

# PATIENT GROUP

## DISEASE BACKGROUND

Sialorrhea is the inability to control saliva accumulation, leading to drooling or dribbling. It can be either anterior - saliva loss onto chin and chest, and/or posterior - pooling at the larynx, with potential aspiration risk.[4]

Drooling is normal in infants, but usually stops as control of the tongue improves and bulbar musculature develops. Excessive drooling is considered abnormal in children over the age of 4 years.[12] However, in patients with neurological disabilities, drooling is common. For children and adolescents with cerebral palsy, sialorrhea is usually caused by disturbed coordination of tongue mobility, lip closure and swallowing, rather than increased saliva production.[13,14]

Chronic sialorrhea can lead to a variety of issues including skin irritation and infection, dehydration, choking, aspiration, pneumonia, and feeding and/or speech problems. Furthermore, it can cause significant embarrassment, and, potentially, social isolation.[4,15]

## CLINICAL NEED AND BURDEN OF DISEASE

Sialorrhea is more common in children with developmental or neurological co-morbidities.[4] Of these, cerebral palsy has been found, in some studies, to be the most common cause of sialorrhea.[16]

There have been varying estimates of sialorrhea prevalence in people with cerebral palsy. A 2010 UK study estimated drooling prevalence in children with cerebral palsy to be 22%.[17] A 2003 UK study found that 58% of the children with cerebral palsy assessed had a drooling condition, including 33% where the drooling was severe.[18] A 2019 meta-analysis (using worldwide studies) estimated that prevalence of drooling in persons with cerebral palsy (across the lifespan) is 44%.[19]

Prevalence of cerebral palsy in children and young people (aged under 25 years) in England and Wales has most recently been estimated in 2019 (using 2004-2014 data) as 2.5–3.4 per 1,000 in England and 2.4–3.2 per 1,000 in Wales.[20] It has been estimated, in 2017, that there are currently around 22,100 people aged 3-15 years with cerebral palsy in England and Wales.[21]

22% of 22,100 equates to 4,900 children and adolescents in England and Wales with cerebral palsy who may have issues with sialorrhea. If the figure of 44% is used, that equates to 9,800.

Prevalence data regarding sialorrhea associated with other neurological disorders and intellectual disability for children and adolescents aged 2 – 17 years is not available.[22]

# PATIENT TREATMENT PATHWAY

## TREATMENT PATHWAY

After detailed assessment, management of sialorrhea in children and adolescents is tailored to each individual, aiming to improve quality of life. There are broadly five types of management strategy[4]:

- Conservative strategies, which focus on oral health, diet, reducing exacerbating factors, and saliva-removal techniques (such as dabbing with wristbands).
- Oral-motor strategies include tongue and mouth exercises, and behavioural interventions, but are only suitable for some patients.
- Pharmacological management is usually anticholinergic.
- Management using botulinum toxin A injection into salivary gland (off-label).
- Finally, surgical management is an option if other strategies have had an insufficient response, or for patients who would need life-long therapy.

## CURRENT TREATMENT OPTIONS

Currently, the main medications used to treat sialorrhea are anticholinergic drugs.[4] For children and young people with cerebral palsy, NICE recommend considering: enteral glycopyrronium bromide, transdermal hyoscine hydrobromide patches, or enteral trihexyphenidyl-benzhexol hydrochloride (particularly if sialorrhea is associated with a dystonic pattern of movement disorder). Only glycopyrronium bromide is currently licensed for sialorrhea (for patients aged 3 years and older); other drugs are used off-label.[6,7]

If anticholinergic drugs provide insufficient benefit or are not tolerated, NICE currently recommend considering specialist assessment and off-label use of botulinum toxin A injections to the salivary glands with ultrasound guidance.[7]

## PLACE OF TECHNOLOGY

If licensed, Xeomin will be more accessible as another treatment option for the management of chronic sialorrhea in children and adolescents aged 2 to 17 years.

# CLINICAL TRIAL SUMMARY INFORMATION

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| **Trial** | **SIPEXI**, NCT02270736, EudraCT 2013-004532-30; Prospective, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study With an Open-label Extension Period to Investigate the Efficacy and Safety of NT 201 in the Treatment of Children and Adolescents (2-17 Years) With Chronic Troublesome Sialorrhea Associated With Neurological Disorders, and/or Intellectual Disability<br>**Phase III - Completed**<br>**Location(s):** EU (not incl UK), Georgia, Russian Federation, Serbia, Ukraine |
| **Trial design** | Randomised, parallel assignment, placebo-controlled, double-blind |
| **Population** | N=256; subjects with chronic troublesome sialorrhea associated with neurological disorders and/or intellectual disability; aged 2 to 17 years old. |
| **Intervention(s)** | Xeomin intraglandular injection |

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| **Comparator(s)** | Matched placebo |
| **Outcome(s)** | Primary outcomes:<br>• Change in unstimulated salivary flow rate [uSFR] from baseline to week 4 [Time frame: Baseline to week 4]<br>• Global Impression of Change Scale [GICS] at week 4 representing the functional improvement in drooling since baseline as assessed by the carer/parent(s) [Time frame: week 4]<br>• Occurrence of treatment emergent adverse effects [TEAEs] overall and by injection cycle. [Time frame: Baseline up to week 64]<br><br>See trial record for full list of all outcomes. |
| **Results (efficacy)** | See trial record on registry |
| **Results (safety)** | See trial record on registry |

# ESTIMATED COST

The exact cost of Xeomin for this intervention is not yet known, but Xeomin 50 unit powder for solution for injection vials have an NHS indicative cost of £72, and Xeomin 100 unit powder for solution for injection vials have an NHS indicative cost of £129.[23]

There is a simple discount patient access scheme for Xeomin in place for treating sialorrhea in adults.[8]

# RELEVANT GUIDANCE

## NICE GUIDANCE

- NICE guideline. Cerebral palsy in under 25s: assessment and management (NG62). January 2017.
- NICE evidence summary: Severe sialorrhoea (drooling) in children and young people with chronic neurological disorders: oral glycopyrronium bromide (ES5). February 2017.

## NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Paediatric Neurosciences - Neurodisability. E09/S/c.

## OTHER GUIDANCE

- American Academy for Cerebral Palsy and Developmental Medicine (AACPDM). Care Pathways: Sialorrhea in Cerebral Palsy. 2018.[24]

# ADDITIONAL INFORMATION

# REFERENCES


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