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Clostridium botulinum neurotoxin A (Xeomin) for lower limb spasticity due to cerebral palsy – first line

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LAY SUMMARY

Cerebral palsy (CP) is a lifelong condition that affects movement and co-ordination, caused by a problem with the brain that occurs before, during or soon after birth. Symptoms are normally noticeable during the first two or three years of life. These may include developmental delay, stiffness or floppiness, weak arms or legs, fidgety, jerky, clumsy, random or uncontrolled movements, problems in walking, swallowing, speaking, and learning disabilities. Most of the children with CP have spasticity which is an increase in muscle tone. It causes degrees of difficulty in moving the body, which may be mild or severe. Effective management of spasticity and other motor problems could be important in preventing functional decline. Although the incidence of CP has remained unchanged in the past four decades but it is expected to rise in the future.

Botulinum toxin type A is a drug that is already in use in the UK for the treatment of a number of disorders including spastic muscular and movement conditions. It acts by selectively blocking the release of a type of enzyme (acetylcholine) involved in spasticity in the muscle. It is administered directly into the affected muscle, providing a temporary reduction in muscular activity in the injected muscles therefore relieving spasticity. If licensed botulinum neurotoxin type A will offer an additional treatment option for lower limb spasticity in children with cerebral palsy.

TARGET GROUP

Lower limb spasticity due to cerebral palsy in children – first line.

TECHNOLOGY

DESCRIPTION

Botulinum neurotoxin type A (Xeomin) is one of the 7 different serotypes of botulinum toxin (A to G) produced by the anaerobic bacterium Clostridium botulinum. Botulinum toxin type A selectively blocks the release of acetylcholine at the cholinergic nerve terminal, ensuring a temporary reduction in muscular activity in the injected muscles[1] and therefore relieves spasticity.

In the trial NCT01893411, in the first arm, patients received 16 Units per kg body weight botulinum neurotoxin type A (high dose) intramuscularly. In the second arm, patients received 12 Units per kg body weight botulinum neurotoxin type A (mild dose) intramuscularly. In the third arm, patients received 4 Units per kg body weight botulinum neurotoxin type A (low dose) intramuscularly.[2]

Botulinum neurotoxin type A is indicated in the UK for:[3]

- Treatment of focal spasticity (including hand and wrist disability associated with stroke)
- Blepharospasm
- Hemifacial spasm
- Spasmodic torticollis
- Severe hyperhidrosis of the axillae
- Prophylaxis of headaches in adults with chronic migraine
- Temporary improvement of moderate to severe wrinkles between the eyebrows in adults under 65 years
- Ankle disability due to lower limb spasticity associated with stroke
- Management of bladder dysfunctions
- Temporary improvement of moderate to severe crow's feet.

Common side effects include paralysis of distant muscles in excessive doses, increased electrophysiologic jitter in some distant muscles and influenza-like symptoms.

Botulinum neurotoxin type A is licensed in the EU for blepharospasm and spasmodic torticollis.[4]

It is currently undergoing phase II trials for:[5]

- Trigeminal neuralgia
- Restless leg syndrome
- Essential tremor
- Bone disorders

It is also undergoing phase III trials for lower and upper limb spasticity and sialorrhea.[5]

INNOVATION and/or ADVANTAGES

If licensed botulinum neurotoxin type A will offer an additional treatment option for lower limb spasticity in children with cerebral palsy.

DEVELOPER

Merz Pharma

PATIENT GROUP

BACKGROUND

Cerebral palsy (CP) is the name for a group of lifelong conditions that affect movement and co-ordination, caused by a problem with the brain that occurs before, during or soon after birth. The symptoms of cerebral palsy aren't usually obvious just after a baby is born. They normally become noticeable during the first two or three years of a child's life. Symptoms can include delays in reaching development milestones, seeming too stiff or too floppy, weak arms or legs, fidgety, jerky or clumsy movements, random, uncontrolled movements, walking on tip-toes, a range of other problems – such as swallowing difficulties, speaking problems, vision problems and learning disabilities.[6]

The NHS describes three different categories of CP:[7]

- Spastic Cerebral Palsy which affects muscle stiffness or weakness.
- Athetoid Cerebral Palsy which affects muscle tone causing involuntary spasms
- Ataxic Cerebral Palsy which affects balance and coordination

It is also possible to have a combination of categories which is referred to as 'Mixed Cerebral Palsy'.

According to NHS England, around 40% of children with CP were born prematurely. In many of these children the precise cause of cerebral palsy is not apparent, but various risk factors can be identified, including maternal illness and postnatal events.[8]

Although in CP, the causative brain damage is static, the motor manifestations change over time. Up to 80% of children with cerebral palsy have a spastic motor impairment. Depending on which parts of the motor cortex are damaged, the imbalance between flexor and extensor muscles may lead to abnormal posture of the joints. The functional abilities of children with spasticity often deteriorate over time. Effective management of spasticity and other motor problems could be important in preventing functional decline.[8]

CLINICAL NEED and BURDEN OF DISEASE

Prevalence of CP in the UK is 3/1000 live births.[9] Cumulative survival estimates up to the age of 16 years in children with CP differ significantly by severity, ranging between 97 per cent and 100 per cent for children with non-severe CP, and between 64 per cent and 67 per cent for those with the most severe CP.

By the end of 2013, the estimated number of children aged three to 15 years living with CP in England and Wales was thought to be about 20,500 rising to approximately 22,100 by 2020, a 7.5 per cent increase. Owing to an increasing population, the number of children living with CP in England and Wales will increase by 2020.[10]

Spasticity is present in around 75-88% of people with cerebral palsy.[11] It causes degrees of difficulty in moving the body, which may be mild or severe. People with spastic CP have a tendency to remain

in certain positions and also to develop shortening of some muscles. This can sometimes limit the movement of joints.[12]

The Hospital Episodes Statistics for England 2016/2017 recorded 956 finished consultant episodes (FCE), 931 hospital admissions and 1,639 FCE beds due to other cerebral palsy (ICD-10 code G80.8).[13]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Spasticity (after stroke) – botulin toxin type A [ID768] (GID-TAG499). Expected date of issue to be confirmed.
- NICE clinical guideline. Spasticity in under 19s: management (CG145). November 2016.
- NICE quality standard. Cerebral palsy in children and young people. (QS162). October 2017.
- NICE interventional procedure guidance. Selective dorsal rhizotomy for spasticity in cerebral palsy (IPG373). December 2010.
- NICE guideline. Cerebral palsy in under 25s: assessment and management. (NG62). January 2017

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Paediatric Neurosciences: Neurorehabilitation. E09/S/d.
- NHS England. 2013/14 NHS Standard Contract for Paediatric Neurosciences: Neurodisability. E09/S/c
- NHS England. 2013/14 NHS Standard Contract for Specialized Rehabilitation for Patients with Highly Complex Needs (All ages). D02/S/a.
- NHS England. 2013/14 NHS Standard Contract for Paediatric Neurosciences: Neurology. E09/S/b.
- NHS England. Clinical Commissioning Policy: Selective Dorsal Rhizotomy for Spasticity in Children with Cerebral Palsy. NHSCB/E09/PS/a. April 2013.
- NHS England. Clinical Commissioning Policy: Cerebellar Stimulator Implants. NHSCB/D04/PS/b

OTHER GUIDANCE

- Russman, B.S., Tilton, A. and Gormley, M.E. Cerebral palsy: a rational approach to a treatment protocol, and the role of botulinum toxin in treatment. *Muscle & nerve*. 1997: 20(S6), 181-193.[14]
- Pavone, V., Testa, G., Restivo, D.A., Cannavò, L., Condorelli, G., Portinaro, N.M. and Sessa, G., 2016. Botulinum toxin treatment for limb spasticity in childhood cerebral palsy. *Front. Pharmacol*. 2016; 7:29.[15]

CURRENT TREATMENT OPTIONS

The aims of managing spasticity are to minimise the effect that it has on the child – to treat pain, improve motor function, improve ease of care, and prevent the consequences of spasticity. In combination with other interventions dealing with the child's associated motor disorders and co-morbidities, the aim is to promote independence and to achieve as complete an integration into

society as possible for the affected child or young person. Many treatments are used in the management of spasticity, with considerable variation in practice. These include:[8]

- Physiotherapy
- Orthoses and aids
- Abnormal stretch reflex modulating interventions:
  - Oral anti spastic medications like baclofen
  - Intrathecal baclofen
  - Local injection botulinum toxin A
  - Selective dorsal rhizotomy
- Orthopaedic surgery

EFFICACY and SAFETY	
Trial	Botulinum neurotoxin type A, Xeomin, NCT01893411; children (2-17 years); phase III
Sponsor	Merz Pharma
Status	Complete but unpublished.
Source of Information	Trial registry[2], Global Data[16]
Location	EU (not UK), Russia, Israel, Republic of Korea and Turkey.
Design	Randomised, controlled
Participants	n=311 (enrolled); aged 2-17 years; cerebral palsy; lower limb spasticity
Schedule	Subjects in the first arm received 16 Units per kg body weight botulinum neurotoxin type A (high dose) intramuscularly. Subjects in the second arm received 12 Units per kg body weight botulinum neurotoxin type A (mild dose) intramuscularly. Subjects in the third arm received 4 Units per kg body weight botulinum neurotoxin type A (low dose) intramuscularly.
Follow-up	Active treatment for 72 weeks
Primary Outcomes	• Change From Baseline in the Ashworth Scale (AS) Score of Plantar Flexors of the Primary Body Side • Co-primary Variable: Investigator's Global Impression of Change of Plantar Flexor Spasticity Scale (GICS-PF) of the Primary Body Side
Secondary Outcomes	Change From Baseline in the AS Score of Plantar Flexors of the Nonprimary Body Side Change From Baseline in the AS Score of Plantar Flexors of the Primary Body Side at Day 29 Changes From Baseline in AS Score of Plantar Flexors of the Primary Body Side at Day 57 and Day 85

	Changes From Baseline in AS Score of Knee Flexors or Thigh Adductors Changes From Baseline in Modified Tardieu Scale [MTS] of Plantar Flexor Investigator's, Child's/Adolescent's, and Parent's/Caregiver's Global Impression of Change Scale Investigator's Global Impression of Change of GICS-Plantar-Flexor of Primary Body Side Changes From Baseline in Gross Motor Function Measure [GMFM]-66 Score Change in Scores of Pain Intensity (From Participants) and Pain Frequency (From Parent/Caregiver) Time to Reinjection for Each of the Three Dose Groups Occurrence of Treatment Emergent Adverse Events (TEAEs) Occurrence of Participants With TEAEs of Special Interest Occurrence of Serious TEAEs Occurrence of TEAEs Related to Treatment Occurrence of TEAEs by Worst Intensity Occurrence of TEAEs by Final Outcome Occurrence of TEAEs Leading to Discontinuation
Key Results	At week 4, statistical analysis of subjects in high dose vs low dose and mild dose vs low dose groups revealed insignificant change from baseline in the Ashworth Scale Score for plantar flexors for primary body side. However, the results regarding the investigator's global impression of change of plantar flexor spasticity scale of the primary body side at week 4 showed significant change in the high dose vs low dose group while the group mild dose vs low dose showed no significant change.[2]
Adverse effects (AEs)	In the first arm (high dose) experienced AEs in 4.49% of the subjects. In the second arm (mild dose) experienced AEs in 1.30% of the subjects. In the third arm (low dose) experienced AEs in 7.69% of the subjects.[2]
Expected reporting date	Reported as August 2015

ESTIMATED COST and IMPACT

COST

Xeomin is already marketed in the UK. A 50unit powder for solution for injection vial costs £72.00.[17]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☐ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☒ Other: *improved quality of life for carers, improved patient convenience*

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other:

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☒ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs:

☐ Other reduction in costs:

☐ Other:

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified:

☒ None identified

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