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HEALTH TECHNOLOGY BRIEFING
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Clostridium botulinum type A toxin-haemagglutinin complex (Dysport®) for urinary incontinence

NIHRIO ID	31084	**NICE ID**	10624
Developer/Company	Ipsen Pharma	**UKPS ID**	659425

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

SUMMARY

Clostridium botulinum type A toxin-haemagglutinin complex (Dysport®) is currently in clinical development for urinary incontinence in adults with neurogenic detrusor overactivity (NDO), as a result of spinal cord injury or multiple sclerosis (MS). Damage to the spinal cord, via MS or injuries, can disrupt communication between the spinal cord and bladder causing NDO. NDO increases pressure in the bladder and decreases the volume of urine the bladder can hold, leading to unexpected and frequent urine leakage (urinary incontinence).

Clostridium botulinum type A toxin-haemagglutinin complex is an injectable drug made from the bacteria that causes botulism. It can block the transmission between nerves and muscles causing a reduction in muscle activity and potentially aid the overactive muscles in the bladder that cause urinary incontinence. If licenced, clostridium botulinum type A toxin-haemagglutinin complex would provide a treatment option for adult patients with urinary incontinence from NDO, as a result of spinal cord injury or MS.

PROPOSED INDICATION

Treatment of urinary incontinence in adults subjects with neurogenic detrusor overactivity (NDO) due to spinal cord injury or multiple sclerosis.[1,2]

TECHNOLOGY

DESCRIPTION

Clostridium botulinum type A toxin-haemagglutinin complex (Dysport®, abobotulinumtoxinA) blocks peripheral cholinergic transmission at the neuromuscular junction by a presynaptic action at a site proximal to the release of acetylcholine. The toxin acts within the nerve ending to antagonise those events that are triggered by Ca^{2+} which culminate in transmitter release. It does not affect postganglionic cholinergic transmission or postganglionic sympathetic transmission.[3]

The action of the toxin involves an initial binding step whereby the toxin attaches rapidly and avidly to the presynaptic nerve membrane. Secondly, there is an internalisation step in which toxin crosses the presynaptic membrane, without causing onset of paralysis. Finally, the toxin inhibits the release of acetylcholine by disrupting the Ca^{2+} mediated acetylcholine release mechanism, thereby diminishing the endplate potential and causing paralysis. Recovery of impulse transmission occurs gradually as new nerve terminals sprout and contact is made with the postsynaptic motor endplate, a process which takes 6 - 8 weeks in the experimental animal.[3]

In the phase III clinical trial (NCT02660359), participants were administered clostridium botulinum type A toxin-haemagglutinin complex 600 Units or 800 Units in two treatment periods (initial and retreatment phase) at 30 injection points.[1]

INNOVATION AND/OR ADVANTAGES

Initial treatment for NDO comprises anticholinergics (ACs) usually in conjunction with clean intermittent catheterisation (CIC). However, the use of ACs frequently results in side-effects, such as dry mouth and constipation, which lead to poor patient compliance and treatment discontinuation. Botulinum toxin A injection in the detrusor is an effective minimally invasive, second-line treatment to reduce incontinence rates.[4]

Dysport is a freeze-dried preparation of abobotulinum toxin-A, that is derived from a different bacterial strain, has a different molecular weight and a different manufacturing process than the botulinum toxin type A (onabotulinumtoxinA) currently used in the second-line treatment of patients with NDO.[5,6] It is important to note that dose ranges are not interchangeable between different botulinum toxin type A containing products.

Studies on Dysport have shown improvements in clinical and urodynamic parameters using 500–1,000 Units in patients with NDO refractory to AC and a favourable benefit to risk ratio was reported with the 750 Units dose.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Clostridium botulinum type A toxin-haemagglutinin complex is licensed for the following indications in the EU/UK:[3]

- Symptomatic treatment of focal spasticity of
  - Upper limbs in adults
  - Lower limbs in adults affecting the ankle joint due to stroke or traumatic brain injury
  - Dynamic equinus foot deformity in ambulant paediatric cerebral palsy patient, two years of age and older
  - Upper limbs in paediatric cerebral palsy patients, two years of age and older
- Symptomatic treatment of
  - Spasmodic torticollis
  - Blepharospasm
  - Hemifacial spasm
  - Severe primary hyperhidrosis of the axillae, which does not respond to topical treatment with antiperspirants or antihidrotics.

Very common adverse effects associated with clostridium botulinum type A toxin-haemagglutinin complex depends on the specific indication and include:[3]

- Dysphagia, dry mouth and muscle weakness when used for spasmodic torticollis
- Ptosis when used for blepharospasm and hemifacial spasm

Clostridium botulinum type A toxin-haemagglutinin complex is in clinical trials for several indications including pain, overactive bladder, obesity and various musculoskeletal disorders.[7]

PATIENT GROUP

DISEASE BACKGROUND

NDO is a consequence of a neurological condition, such as a spinal injury or multiple sclerosis (MS). People with a spinal injury have irreversible nerve damage, while people with MS develop lesions in the spinal cord caused by the progression of the disease. In both cases, communication between the spinal cord and the bladder becomes disrupted or broken, leading to overactivity of the detrusor muscles and resulting in unregulated sporadic bladder muscle contractions. The problem increases pressure in the bladder and decreases the volume of urine the bladder can hold, leading to unexpected and frequent urine leakage.[8] This in turn can result in recurrent bladder infections, stones, hydronephrosis, pyelonephritis, and renal failure.[9]

Urinary incontinence is believed to have a greater social impact than any other MS symptom or complication when it comes to quality of life. It discourages people from engaging in outdoor activities and affects their ability to work. While the symptom can be caused by urinary tract infections, which are common in MS, urinary incontinence can be the result of NDO.[8]

CLINICAL NEED AND BURDEN OF DISEASE

Approximately 75% of patients with MS experience lower urinary tract symptoms.[10] There are an estimated 105,780 MS patients in the UK,[11] meaning that there may be an estimated 79,350 patients with MS experiencing lower urinary tract symptoms including those related to NDO and urinary incontinence.

Approximately 81% of individuals with a spinal cord injury are reported to have neurogenic bladder problems.[12] It is estimated that there are around 50,000 patients living with a spinal cord injury in the UK.[13] As a result, there may be an estimated 40,500 patients with neurogenic bladder problems related to NDO and urinary incontinence with spinal cord injury in the UK.

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatments to improve bladder storage for urinary incontinence in neurological disease include behavioural management programmes (for example, timed voiding, bladder retraining or habit retraining), antimuscarinic drugs and botulinum toxin type A injections. Pharmacological treatments may also be given to prevent urinary tract infection, improve bladder emptying and for stress incontinence.[14]

Other traditional bladder management options may be a switch to reflex voiding with or without a sphincterotomy, bladder augmentation or urinary diversion. These options are frequently not acceptable to many individuals with NDO because they involve surgery or wearing a urinary device.[6]

CURRENT TREATMENT OPTIONS

NICE recommends bladder wall injection with botulinum toxin type A to adults:[14]

- with spinal cord disease (for example, spinal cord injury or multiple sclerosis) and
- with symptoms of an overactive bladder and
- in whom antimuscarinic drugs have proved to be ineffective or poorly tolerated

Since publication of the guidance only Botox has been approved for NDO with urinary incontinence due to subcervical spinal cord injury (traumatic or non-traumatic), or multiple sclerosis, use of other botulinum toxin type As is off label.[14,15]

PLACE OF TECHNOLOGY

If licenced, clostridium botulinum type A toxin-haemagglutinin complex would provide a treatment for urinary incontinence in adults subjects with NDO due to spinal cord injury or multiple sclerosis.[1,2]

CLINICAL TRIAL INFORMATION

Trial	**CONTENT1;** NCT02660138, 2015-003471-30; A Phase III, Multicentre, Randomised, Double Blind, Parallel Group, Placebo Controlled Study To Assess The Efficacy And Safety Of One Or More Intradetrusor Treatments Of 600 Or 800 Units of Dysport® For The Treatment Of Urinary Incontinence In Subjects With Neurogenic Detrusor Overactivity Due To Spinal Cord Injury Or Multiple Sclerosis **Phase III** - Terminated **Location(s):** 6 EU countries, USA, Canada, Turkey and the Republic of Korea. **Study completion date:** February 2019
Trial design	Randomised, parallel assignment, double-blinded
Population	N = 227 (actual), Urinary Incontinence for at least 3 months prior to Screening as a result of NDO due to Spinal Cord Injury or MS, aged 18 years to 80 years.

Intervention(s)	800 or 600 units intra detrusor injection in two treatment periods (Initial and Retreatment phase) delivered at 30 injection points
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome(s); - Change in weekly number of UI episodes [Time Frame: Baseline, 6 weeks] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**CONTENT2**; NCT02660359, 2015-000507-44; A Phase III, Multicentre, Randomised, Double Blind, Parallel Group, Placebo Controlled Study To Assess The Efficacy And Safety Of One Or More Intradetrusor Treatments Of 600 Or 800 Units Of Dysport® For The Treatment Of Urinary Incontinence In Subjects With Neurogenic Detrusor Overactivity Due To Spinal Cord Injury Or Multiple Sclerosis **Phase III** - Terminated **Location(s):** 5 EU countries, UK, and other countries. **Study completion date:** July 2019
Trial design	Randomised, parallel assignment, double-blinded
Population	N = 258 (actual), Urinary Incontinence for at least 3 months prior to Screening as a result of NDO due to Spinal Cord Injury or MS, aged 18 years to 80 years.
Intervention(s)	800 or 600 units intra detrusor injection in two treatment periods (Initial and Retreatment phase) delivered at 30 injection points
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome(s); - Change in weekly number of UI episodes [Time Frame: Baseline, 6 weeks] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

Clostridium botulinum type A toxin-haemagglutinin complex (Dysport) is already marketed in the UK, the NHS indicative price is:[16]

- £92.40 per 300unit powder for solution for injection vial
- £154.00 per 500unit powder for solution for injection vial.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE clinical guideline. Urinary incontinence in neurological disease: assessment and management (CG148). August 2012.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

No relevant guidance identified.

OTHER GUIDANCE

- Fowler CJ, Panicker JN, Drake M, et al. A UK consensus on the management of the bladder in multiple sclerosis. 2009.[10]

ADDITIONAL INFORMATION

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