National Institute for Health Research

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Cloristridium botulinum Type A toxin (Dysport) for Spasmodic torticollis

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LAY SUMMARY

Dystonia is a condition that causes muscle spasms and stiffening, which sometimes result in abnormal positions. Spasmodic torticollis is a form of dystonia affecting the neck specifically. The causes are not well understood, but in some cases it can be inherited, caused by other medicines, or as a result of another brain disease. Symptoms include muscle spasms causing the neck to be twisted or pulled in different directions, neck pain and stiffness. Most cases of spasmodic torticollis begin in midlife and can last for several years, and sometimes for life.

Clostridium botulinum Type A toxin is a drug which works by preventing muscular spasms from occurring. It is injected directly into the neck muscle. Injections are repeated once the condition begins to worsen again, usually every few months. Clinical trials have shown participants experienced improvements in their condition when given clostridium botulinum Type A toxin compared to placebo. If licensed, this pre-prepared form of clostridium botulinum Type A toxin would reduce the burden on staff to mix and prepare the drug before administering it to patients.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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TARGET GROUP

Spasmodic Torticollis; adults– first line.

TECHNOLOGY

DESCRIPTION

Clostridium botulinum type A toxin-haemagglutinin complex (Dysport; AbobotulinumtoxinA) is a neuromuscular blocking agent which works by inhibiting the release of the neurotransmitter acetylcholine from the cholinergic nerve endings. The toxin binds to the nerve endings and is internalised into the cell by receptor-mediated endocytosis which leads to intracellular blockage of neurotransmitter exocytosis into the neuromuscular junction.[1] Dysport is intended for use in a range of conditions including the treatment of muscular spasm and hyperhidrosis.[2] In the phase III trial clostridium botulinum type A toxin-haemagglutinin complex 250-500 units is administered by intramuscular injection over one or more treatment cycles.[12, 14, 16, 18]

Clostridium botulinum type A toxin-haemagglutinin complex (powder for solution) (Dysport) has been licensed for use in the EU for the symptomatic treatment of:

- Focal spasticity of upper limbs in adults
- Focal spasticity of lower limbs in adults affecting the ankle joint due to stroke or traumatic brain injury
- Dynamic equinus foot deformity in ambulant paediatric cerebral palsy patients (2 years of age or older)
- Spasmodic torticollis (cervical dystonia) in adults
- Blepharospasm in adults
- Hemifacial spasm in adults
- Severe primary hyperhidrosis of the axillae which does not respond to topical treatment with antiperspirants or antihidrotics[2]

Common (prevalence >1/00, <1/10) adverse events reported for clostridium botulinum type A toxin-haemagglutinin complex 500 units across a variety of indications including spasmodic torticollis are asthenia, fatigue, influenza-like illness, injection site reactions (pain, bruising, pruritus and oedema). For spasmodic torticollis specifically, common adverse events reported include headache, dizziness, facial paresis, blurred vision, reduced visual acuity, dysphonia, dyspnoea, dysphagia, dry mouth, muscle weakness, neck pain, musculoskeletal pain, myalgia, pain in the extremity and musculoskeletal stiffness.[2]

Clostridium botulinum type A toxin-haemagglutinin complex is currently in pre-registration for lower limb muscle spasticity, in phase III trials for overactive bladder, urinary incontinence and upper limb muscle spasticity, and in phase II trials for dystonia.[1]

INNOVATION and/or ADVANTAGES

If licensed, this pre-prepared formulation of clostridium botulinum type A toxin-haemagglutinin complex may have the potential to reduce the burden on staff administering this drug to patients with spasmodic torticollis by eliminating the need to prepare powdered clostridium botulinum type A

toxin-haemagglutinin complex for intramuscular injection. This may potentially lead to reduced resources needed for drug preparation.

DEVELOPER

Ipsen Limited.

AVAILABILITY, LAUNCH or MARKETING

Clostridium botulinum type A toxin-haemagglutinin (Dysport) was a designated orphan drug in the USA for Lower Limb Muscle Spasticity on 20 October 1999.

PATIENT GROUP

BACKGROUND

Spasmodic torticollis (cervical dystonia) is a rare neurological disorder and the most common form of focal dystonia, affecting only the neck muscles.[3, 4] It results in mild to severe involuntary muscular contractions and spasms in the neck muscles often causing the neck and head to twist or be pulled forward, backwards or to the side.[4] Other symptoms of spasmodic torticollis are tremor and pain/discomfort due to muscular spasm.[5] Spasmodic torticollis is usually idiopathic, meaning there is no identifiable cause, however genetic susceptibility (evidenced by family history) may be present in 10-25% of cases. Several gene mutations have been associated with spasmodic torticollis: GNAL, THAP1, CIZ1, ANO3. In some cases (secondary spasmodic torticollis) there is an identifiable cause, such as the use of certain drugs with dopamine receptor blocking activity (including antipsychotics or nausea medication) and degenerative brain disease.[3] The majority of cases appear in mid-life and the condition often worsens during periods of stress or while walking and improves with rest, sleep or sensory tricks (e.g. placing a hand on the face, chin or back of the head).[5] Spasmodic torticollis can persist for several years, and sometimes for life, although about 20% of people will recover without treatment.[6]

Spasmodic torticollis can impact quality of life, affecting activities of daily living, including employment.[3] There is an important two-way relationship between spasmodic torticollis and mental health, as symptoms of dystonia can cause anxiety and depression but anxiety and stress can also make physical symptoms worse. It is therefore important that people with spasmodic torticollis and a mental health condition receive appropriate treatment.[7]

CLINICAL NEED and BURDEN OF DISEASE

Spasmodic torticollis affects an estimated 18,000 adults in the UK and 60,000 people in the USA.[3,5] Prevalence of spasmodic torticollis across Europe is reported as 0.006% (5.7 per 100,000).[8]

The UK Hospital Episode Statistics from 2015-16 does not report data on spasmodic torticollis separately, but does report statistics on dystonia in general. In 2015-16 there were 4,102 admissions, 5,442 bed days and 4,408 finished consultant episodes for Dystonia (ICD10 G24).[9]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE interventional procedures guidance. Selective peripheral denervation for cervical dystonia (IPG80). August 2004.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. NHS Standard Contract for Neurosurgery (Adult). D03/S/a.
- NHS England. Clinical Commissioning Policy: Deep Brain Stimulation (DBS) in movement disorders. NHSCB/D03/P/b. April 2013.

OTHER GUIDANCE

- Albanese, A. *et al* (2011), EFNS guidelines on diagnosis and treatment of primary dystonia's. European Journal of Neurology, 18: 5–18.
- The Dystonia Society. Dystonia: A Guide to Good Practice for Health and Social Care Professionals. Available from: http://www.dystonia.org.uk/index.php/professional-research/good-practice-guide.

CURRENT TREATMENT OPTIONS

Most therapies for spasmodic torticollis target symptoms, e.g. relieving spasms, pain and improving posture or function. However, not every treatment option is successful for all spasmodic torticollis patients, therefore several different treatments and approaches may need to be tried before an effective therapy is found for the individual. There are 3 basic treatment options available;[3,5,10]

- Botulinum toxin injections: This is the treatment of choice for spasmodic torticollis, and consists of injecting low doses of botulinum toxin into the neck muscles. Effect begins 2-3 days after injection and last approximately 2-6 months. There are 3 different brands of botulinum toxin A available for use in spasmodic torticollis; BOTOX (onabotulinumtoxinA), Dysport (abobotulinumtoxinA) and Xeomin (incobotulinumtoxinA). All three brands are not interchangeable and are administered as a unique drug; no evidence exists to support the use of one above the other.
- Oral medication: there are several drugs available to reduce spasms and treat symptoms of spasmodic torticollis:
    - Dopaminergic drugs (e.g. Levodopa) – most likely to be effective in children and young adults. It is more often prescribed in people with a family history of early onset dystonia.
    - Anticholinergic drugs (e.g. Trihexydhenidyl, Biperiden, Procycline) – especially helpful for childhood-onset and severe cases of dystonia, although those with adult-onset dystonia may still benefit.
    - GABA agonist (Benzodiazepine, Diazepam, Baclospas, Tizanidine) – inhibit the transmission of nerve signals in the brain, so act as muscle relaxants. These drugs usually benefit children and a minority of adults with focal dystonia.
    - Tetrabenazine, risperidone – help control spasms in severe dystonia.

- Surgery:
    - Selective peripheral denervation – cutting of the nerves leading to the dystonic muscles. Usually an alternative treatment for people who are unresponsive to other treatments.[6]
    - Deep brain stimulation surgery – involves the placement of electrodes into the globus pallidus (on both sides) which deliver small electrical impulses into the brain. Appropriate for patients who lose response to botulinum toxin or have a form of spasmodic torticollis which is difficult to treat with injections.

Other therapies include strategies to support patients to manage their condition and symptoms, including;[5]

- Physiotherapy – delivered by specialist neuro-physiotherapists, rehabilitative physiotherapy aims to give patients increased independence.
- Psychological therapy – e.g. cognitive behavioural therapy, counselling and stress/anxiety management.
- Pain management – as the prevalence of substantial pain is high in spasmodic torticollis, pain management programmes are used to manage chronic pain.
- Dietary support – as treatment with botulinum toxin can cause dysphagia and excessive movement can make eating difficult, dietitians may recommend texture modified (puree) diets, food fortification and nutritional supplement drinks.

EFFICACY and SAFETY

Trial	NCT01753310, A-TL-52120-169; adults with a primary diagnosis of cervical dystonia previously untreated with botulinum toxic; Dysport vs Placebo; phase III	NCT01753336, A-TL-52120-170; adults enrolled in NCT01753310 with no ongoing adverse events; Dysport only; phase III extension
Sponsor	Ipsen Limited	Ipsen Limited
Status	Published in abstract	complete but unpublished
Source of Information	abstract[11], poster[11], trial registry[12]	publication[13], trial registry[14]
Location	USA	USA
Design	Randomised, controlled, parallel assignment study	Non-randomised, uncontrolled, single group assignment study
Participants	N=134; aged 18 years and older; primary cervical dystonia; at least 9 months from onset; previously untreated with botulinum toxin or currently treated with Botox at a total dose 100-200IU and <60IU at last injection cycle and satisfactory response to last 2 sequential Botox treatment cycles	N=112; aged 18 years and older; enrolled in or completed NCT01753310; no ongoing adverse events related to study treatment

Schedule	Randomised to receive a single intramuscular injection of either 250-500IU (in a vial of 2mL dilution) of Dysport or 2mL Placebo.	All participants receive up to 500IU Dysport by intramuscular injection (2mL vial) for three treatment cycles
Follow-up	Active treatment for 1 cycle and overall follow–up period of 4 wks	Active treatment for 3 cycles (12-16 weeks in duration each with an overall follow-up period of 48wks (11 mths)
Primary Outcomes	Change from baseline in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) Total Score at Wk 4.	Change from treatment cycle baseline in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) Total Score at Wks 4 and 12 of treatment cycles 1-3.
Secondary Outcomes	Change From Baseline in TWSTRS Total Score at Wk 2; Change From Baseline in Clinical Global Impression of Change (CGIC) in Cervical Dystonia (CD) at Wk 2; TWSTRS Responders at Wk 2; Change From Baseline in CGIC in CD at Wk 4; TWSTRS Responders at Wk 4; Change From Baseline in Cervical Dystonia Impact Profile-58 (CDIP-58) Total Score at Wk 4; Change From Baseline in CDIP-58 Total Score at Wk 2	TWSTRS Total Scores at Pretreatment Baseline, Wks 4 and 12 for Treatment Cycles 1, 2 and 3; Treatment Response in Treatment Cycle 3 Wk 4; change from treatment cycle baseline to treatment cycles 1, 2 and 3 in: TWSTRS Severity Subscale Score, TWSTRS Disability Subscale Score, TWSTRS Pain Subscale
Key Results	A total of 134 patients (abobotulinumtoxinA n=89, placebo n=45) were randomized and 129 (abobotulinumtoxinA n=84, placebo, n=45) completed the Wk 4 primary endpoint evaluation. Versus placebo, abobotulinumtoxinA patients experienced significantly greater changes from baseline in TWSTRS Score at Wk 4 (-2.5 versus -10.8, *P*<0.001; based upon the modified intent-to-treat population). Adverse events (AEs) occurred in 41% and 22% of abobotulinumtoxinA and placebo patients, respectively.	AbobotulinumtoxinA produced a significant decrease from baseline in mean (±SE) TWSTRS total scores compared with those previously treated with placebo at Wk 4 (primary efficacy endpoint; −15.6 ± 2.0 vs. −6.7 ± 2.0; $p < 0.001$) with significant improvements sustained to Wk 12 ($p = 0.019$). Dysport also produced significant improvements in TWSTRS subscale scores, VAS pain scores, and subject/investigator's VAS symptom assessments compared to those previously treated with placebo. During open-label treatment, all treatment cycles resulted in improvements in mean TWSTRS total and subscale scores at Wk 4 post-treatment; greatest improvement was seen in cycle 1.
Adverse effects (AEs)	Total number of adverse events were n=41 in the abobotulinumtoxinA group and n=22 in the placebo group (p=0.001). Total serious adverse events were n=4 (4.55%) in the abobotulinumtoxinA group vs. n=1 (2.22%) in the placebo group.	The most common treatment-emergent adverse event (TEAE) was dysphagia, which did not appear to be dose dependent; for 500IU, 750IU and 1000IU doses dysphagia was reported in 15%, 17% and 14% respectively. Reported proportions of dysphagia also did not appear to be related to

	Dysphagia was reported in 9% of treated patients. Other AEs in treated patients were muscle weakness, neck pain, and headache, none of which were reported with placebo.	treatment cycle, a 12%, 13%, 6% and 10% at treatment cycle 1, 2, 3 and 4 respectively. Other TEAEs included Injection site pain (5% previously in Abobotulinumtoxin A group vs. 3% previously in placebo group), Upper respiratory tract infection (4% previously in Abobotulinumtoxin A group vs. 3% previously in placebo group), neck pain (5% previously in Abobotulinumtoxin A group vs. 5% previously in placebo group) and headache (4% previously in Abobotulinumtoxin A group vs. 3% previously in placebo group).
Expected reporting date	-	-

Trial	NCT00447772, A-94-52120-098, 2004-002086-20, EudraCT-2004-002086-20; adults above 18 years old; Dysport only; phase III	NCT00257660, Y-47-52120-051, EudraCT-2005-000709-70, 2005-000709-70; adults above 18 years old; Dysport 500IU vs placebo; phase III
Sponsor	Ipsen Limited	Ipsen Limited
Status	published	Published
Source of Information	publication[15], trial registry[16],	publication[17, 13], trial registry[18]
Location	Austria and Germany	USA and Russia
Design	Non-randomised, uncontrolled, open label	Randomised, placebo-controlled, parallel assignment, double blinded
Participants	n=516; aged 18 years and above; de novo patients with cervical dystonia;	N=116; aged 18 years and above; cervical dystonia at least 18 months from since onset; previously untreated with botulinum toxin or previously treated with botulinum toxin Type A or B with a maximum interval of 16 weeks since the last injection and having returned to at least their pre-treatment status
Schedule	Intramuscular injection of Dysport 500IU/2.5ml injected into the muscles involved in cervical dystonia.	Randomisation to receive either Intramuscular injection of Dysport 500IU or placebo
Follow-up	Follow up at 0, 4 and 12 weeks.	Follow up at 2, 8 and 12 weeks
Primary Outcomes	Change in Tsui score from baseline to wk 4	Change in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) Baseline to Wk 4,
Secondary Outcomes	Quality of life at Wks 0, 4, 12, evaluation of efficacy and safety/tolerability by investigator and patient at Wks 4 and 12, dose and injection protocol for any subsequent	change in TWSTRS Baseline to Wk 8, TWSTRS Total Score Baseline and Wk 12, subject Visual Analogue Score (VAS) for Cervical Dystonia (CD) symptom

	injections at Wk 12, descriptive analysis of subgroups at Wks 0, 4 and 12, sitting Tsui score profile at Wks 0, 4 and 12, walking Tsui score at Wks 0, 4 and 12, comparison of Tsui scores with patient sitting and patient walking at Wks 0, 4 and 12.	assessment Baseline to Wk 4, 8 and 12, investigator VAS for CD symptom assessment Baseline to Wk 4, 8 and 12, SF-36 Mental Health Summary Score at Wk 8, number of participants considered by the investigator to be overall treatment successes at Wk 12.
Key Results	Treatment with Dysport significantly reduced mean Tsui scores from baseline to wk 4 (−3.83; 95% CIs −4.01 to −3.57; p<0.0001), corresponding to a percentage improvement of 44.3±34.8%. The mean changes in Tsui subscale scores from baseline to wk 4 were statistically significant for all Tsui subscores: Amplitude of rotation, deflection (tilt) and ante-/retrocollis (−1.4; 95% CI −1.5 to −1.3), duration of movement (−0.3; 95% CI −0.4 to −0.3), duration of shoulder elevation, (−0.4; 95% CI −0.5 to −0.3), tremor, (−0.6; 95% CI −0.7 to −0.5).[20]	There were significant differences in change from baseline to wk 4 between Dysport (n=55) and placebo (n=61) treatment groups for VAS Score (17.7 ± 24.4 vs -4.8 ± 24.6, p=0.0013) and TWSTRS pain subscale (-3.7 ± 4.7 vs. -1.3 ±3.8, p= 0.0017). Improvements in all eight SF36 domains were seen in Dysport treated participants compared to placebo (where improvement was seen in 6 out of 8 SF36 domains). However there was no significant difference between Dysport and placebo treated participants for 3 SF36 domains (vitality, social functioning and mental health).[19]
Adverse effects (AEs)	Of the 515 people who took part in the trial 213 (41.4%) experiences an AE. The most common AEs were muscular weakness, dysphagia and neck pain (occurring in 13.8%, 9.9% and 6.6% of participants respectively).[20]	Total number of AEs experienced (excluding serious AEs) were 11/55 (20%) in the Dysport group compared to 5/61 (8.2%) in the placebo group. The most common AE in the Dysport group was dysphagia, occurring in 9.1% of participants (compared to 0% in placebo participants). Injection site and neck pain occurred in 5.5% and 5.5% of Dysport participants respectively and 3.3% and 4.9% of placebo participants respectively. Serious AEs occurred in 1 placebo participant (suicide attempt).[21]
Expected reporting date	-	-

ESTIMATED COST and IMPACT

COST

Clostridium botulinum type A toxin-haemagglutinin complex 500 units (Dysport) is already marketed in the UK; a 500 unit vial (of powder for reconstitution) costs £154.00.[22]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☐ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ 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: *reduced need for drug preparation before administration, less staff required to prepare drug for administration*

☐ 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: *potentially less staff/time needed to prepare drug for administration*

☐ Other

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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