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HEALTH TECHNOLOGY BRIEFING
JULY 2021

Dronabinol for muscle spasticity caused by multiple sclerosis

NIHRIO ID	27002	**NICE ID**	10638
Developer/Company	Canopy Growth	**UKPS ID**	N/A

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Dronabinol is in clinical development for the treatment of spasticity caused by multiple sclerosis (MS). MS is a long-term condition that affects the brain and spinal cord, causing a range of symptoms including spasticity. Spasticity is when the muscles become stiff and resistant to movement, which can be extremely painful. There are currently limited treatment options for patients with spasticity caused by MS.

Dronabinol, administered orally, is a synthetic (artificial) form of the psychoactive component of cannabis, which means it can cause changes to cognitive/emotional processes and reduces pain. Dronabinol may reduce spasticity although the precise mechanism for this effect has not been elucidated. If licensed, dronbionol will offer an additional treatment option for adults with spasticity caused by MS.

PROPOSED INDICATION

Treatment of adults with muscle spasticity due to MS – third-line.[1]

This briefing reflects the evidence available at the time of writing 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. A version of the briefing was sent to the company for a factual accuracy check. The company was unavailable to comment.

TECHNOLOGY

DESCRIPTION

Dronabinol (BX-1) is a synthetic form of delta-9-tetrahydrocannabinol (Δ9- THC), the primary psychoactive component of cannabis. The effect of THC is demonstrated through its partial and weak agonist activity at both the cannabinoid-1 and cannabinoid-2 receptors (CB1R and CB2R, respectively), therefore resulting in the well known effects cannabis smoking can cause such as changes in cognitive and emotional processes, reduced pain and increased appetite.[2] The precise mechanism by which Dronabinol may reduce spasticity is unknown, although animal studies have identified CB1 as the receptor that mediates the antispasticity actions of cannabinoids.[3]

Dronabinol is currently phase III clinical development for the treatment of adults with muscle spasticity caused by multiple sclerosis. In the phase III cinical trial (NCT03756974), participants will receive dronabinol orally.[1]

INNOVATION AND/OR ADVANTAGES

It has been demonstrated that cannabinoids target CB1 receptors to induce an antispastic effect on muscles. Currently, the licensed therapy for MS patients with muscle spasticity is a oromucosal spray containing delta-9-tetrahydrocannabinol-cannabidiol (THC-CBD). However, there are currently no licensed oral solution cannabinol formulations. If approved, dronabinol would offer a new formulation of cannabinol treatment for patients with muscle spasticity caused by multiple sclerosis.[4,5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Currently dronabinol does not have marketing authorisation in the EU/UK for any indication.

Dronabinol is currently in phase II and phase III clinical development for the treatment of agitation in Alzheimers disease, nightmares in post-traumatic stress disorder, acute pain following traumatic injury, and postoperative pain in total joint arthroplasty.[6]

PATIENT GROUP

DISEASE BACKGROUND

MS is a lifelong condition that can affect the brain and spinal cord, causing a wide range of potential symptoms, including problems with arm or leg movement, vision, balance or sensation. The clinical course of MS is highly heterogeneous.[7] Exactly why someone develops MS isn't known. It is not caused by lifestyle factors and it is not clear whether it can be prevented.[8]

Amongst the many symptoms of MS is muscle spasticity, which is a common symptom of MS. Spasticity is when the muscles become stiff and resistant to movement.[7] Spasticity is caused by an increase in muscle tone. Muscle tone is the resistance to movement in a muscle or the level of tension.[9] Muscle tone can stem from a wide range of involuntary and sustained muscle

contractions or sudden movements (spasms). Muscle spasticity can be a mild such as the feeling of tightness in muscles or it can be severe and produce uncontrollable, painful spasms of extremities, most commonly in the legs.[10] There are different forms of spasticity; flexor, extensor and adductor spasticity.

In extensor spasticiy, the limbs are difficult to bend as the muscles are very tight. In flexor spasticity, the limbs are bent and straightening them is difficult due to the tightness of the muscles. An adductor spasm causes the limb to pull in towards the body therefore causing difficulty to separate the limbs such as the thighs.[9] Spasticity can be aggravated by position changes or sudden movements, humidity, extremes of temperatures or infections and may even be triggered by tight clothing.[10] Other trigger factors include other MS symptoms such as bladder or bowel problems or pain.[9]

CLINICAL NEED AND BURDEN OF DISEASE

In England, the estimated prevalence of MS is 190 cases per 100,000 population, with 105,800 individuals in England having been diagnosed with MS. MS is more than twice as common in females than males (272 versus 106 per 100,000 population, respectively). It is estimated by the Multiple Sclerosis Society that around 110,000 people are living with MS in the UK and there are around 5,200 new cases of MS diagnosed each year.[9]

According to the Hosptal Episodes Statistics (ICD-10: G35) data in 2019-20, in England, there were 51, 632 finished consultant episodes (FCEs), 49, 037 admissions, resulting in 54, 249 FCE bed days and 43, 875 day cases for primary diagnosis of multiple sclerosis.[11]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

There is currently no cure for MS, but it is possible to treat the symptoms with medicines and other treatments. People who are suspected to have MS will be referred to a consultant neurologist. There are two main approaches to treating MS; disease modifying therapies and management of MS symptoms. Disease modifying therapies, administered by neurologists, aim to reduce the number of relapses experienced, to reduce the severity of these relapses and reduce disability progression and MRI activity. However, they cannot reverse existing damage. Management of MS symptoms can be overseen by specialist referrals as appropriate.[12,13]

The majority of treatment for MS involves the management of MS symptoms. These include cognition, emotional lability, incontinence, mobility and fatigue, oscillopsia, pain and spasticity. The treatments given to manage symptoms may include drug therapies, self-management strategies or different types of therapies.[13] Official guidelines recommend that everyone with MS has a review with their specialist at least once a year. It should be decided together with a specialist what the treatment plan should be.[14] Managing the factors that trigger spasticity, incorporating stretches and maintaining good posture can aid in the reduction of the effects of spasticity without the need of medication. The use of medication is only effective if the trigerring factors of spasticity are also being addressed.[15]

CURRENT TREATMENT OPTIONS

Currently for the management of MS and the treatment of muscle spasticity, NICE recommends:[16]

- consideration of benzodiazepines as a third-line option to treat spasticity in MS
- a 4-week trial of THC-CBD spray if: other pharmacological treatments for spasticity are not effective; after the 4-week trial, THC-CBD spray should continue to be used if the person has had at least a 20% reduction in spasticity-related symptoms on a 0 to 10 patient-reported numeric rating scale.[17]

PLACE OF TECHNOLOGY

If licensed, dronabinol will offer an additional treatment option for patients with muscle spasticity caused by multiple sclerosis.

CLINICAL TRIAL INFORMATION

Trial	**DrosSpas-1** NCT03756974**;** A Phase III, Multi-centre, Randomised, Double-blind, Placebo-controlled, Parallel-group Clinical Trial to Investigate the Efficacy and Safety of BX-1 for the Symptomatic Relief of Spasticity in Patients With Multiple Sclerosis (MS) **Trial phase** – Phase III **Location(s):** 5 EU countries **Study completion date:** March 30, 2021
Trial design	Multi-centre, randomised, parallel assignment, quadruple-blinded
Population	n=397 (actual); aged 18 to 65 years with the presence of MS and stable MS for at least 3 months; ongoing spasticity in at least 2 lower limb muscles for at least 3 months before enrolment; received previous treatment with at least two different optimized oral MS anti-spasticity therapies before inclusion. Both treatment attempts must include at least baclofen or oral tizanidine, which can be combined with other anti-spasticity drugs and patients currently receiving an optimised treatment corresponding to the last treatment attempt with stable dosage for at least 30 days prior to Visit 0;
Intervention(s)	Participants will receive dronabionol, orally. All patients enrolled establish their individually tolerable dose by dose titration.
Comparator(s)	Matched placebo
Outcome(s)	Responder analysis: proportion of patients showing improvement in spasticity of 18% or more in average

	Numerical Rating Scale for Spasticity (NRS-S) assessment at end of treatment [Time Frame: 16 weeks] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of dronabinol is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Multiple sclerosis in adults: management (CG186). October 2014.
- NICE quality standard. Multiple sclerosis (QS108). January 2016.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. Treatment Algorithm for Multiple Sclerosis Disease-Modifying Therapies (NHS England Reference: 170079ALG). London: NHS England; 2019.

OTHER GUIDANCE

- Multiple Sclerosis: National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care. 2004.[18]
- Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis. 2018.[19]

ADDITIONAL INFORMATION

Canopy Growth did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

REFERENCES

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