MTRAC
Midlands Therapeutics Review and Advisory Committee

COMMISSIONING GUIDANCE
Cannabis extract
(Sativex®▼)

For the management of spasticity in multiple sclerosis

BNF: 10.2.2

Prescribing guidance: Category D *(cannot be recommended for prescribing because of inadequate evidence for efficacy and/or safety)*

Sativex cannot be recommended for prescribing because the current evidence for its efficacy and safety is considered to be inadequate to support its use. Results from published comparisons of Sativex with placebo for the treatment of spasticity in patients with multiple sclerosis were inconsistent. Limitations of the trials included definitions of disease severity and outcome measures not commonly used in clinical practice, and small effect sizes. No published trials have compared Sativex with an active comparator.

Commissioning guidance:

In view of the decision by the Committee that Sativex could not be recommended for prescribing, no further commissioning advice was considered necessary.

Objectives

- To appraise the clinical evidence for the efficacy and safety of Sativex for the treatment of spasticity in patients with multiple sclerosis (MS)
- To estimate the potential cost impact
- To provide prescribing and commissioning guidance

Description of technology

Sativex is a mixture of two extracts of the *Cannabis sativa L.* plant: delta-nine tetrahydrocannabinol (THC, 27 mg/ml) and cannabidiol (CBD, 25 mg/ml) delivered as a 100 microlitre dose via an oromucosal spray. It acts on cannabinoid receptors in the central nervous system; this activity has been shown in animal models to ameliorate limb stiffness and improve motor function.[1] It is licensed for use as add-on treatment for symptom improvement in patients with moderate to severe spasticity due to MS who have not responded adequately to other anti-spasticity medication, and who demonstrate clinically significant improvement in spasticity-related symptoms during an initial trial of therapy.[1] Sativex was launched in the UK in June 2010.

Background

Multiple sclerosis is an autoimmune disease of the central nervous system in which inflammation destroys the protective sheath surrounding nerve cells. Estimates of the percentage of patients with MS who experience symptoms of spasticity vary from 21% to 84%.[2,3] This loss of muscle control can lead to pain, spasms, reduced mobility, limited range of movement and contractures.[4]

The NICE clinical guideline on multiple sclerosis,[2] published in 2003, recommends physiotherapy as a first-line option for patients with persistent spasticity or spasms. Specific measures such as drug treatment should be considered only if the spasms or spasticity are causing pain or distress. Recommended options for initial drug treatment are baclofen or gabapentin *[unlicensed indication].* If these treatments are unsuccessful or not well tolerated, then tizanidine, diazepam, clonazepam or dantrolene are further options. NICE guidance on Sativex is expected in January 2012.[5]

Appraisal of clinical evidence for efficacy and safety

Three published, double-blind RCTs compared Sativex with placebo in a total of 767 patients with MS and symptoms of spasticity that had not responded to current therapy.[6-8] The trials were of six to fifteen weeks' duration. One of the trials used a two-phase 'enriched' design. In this trial, 572 patients were first enrolled in a four-week single-blind screening phase where all patients were given Sativex and only those showing a response to treatment (≥ 20% improvement in NRS spasticity score) were randomised to the double-blind treatment phase.

In all three trials, the mean number of sprays taken per day reported by patients was 8 to 9, although maximum daily doses of up to 12,[8] 24,[7] or 48 sprays[6] were permitted. Patients also continued existing medications, including anti-spasticity treatment. The primary outcome was a patient-rated measure of spasticity severity on a numerical rating scale (NRS) from 0 (no spasticity or stiffness) to 10 (total spasticity or stiffness). A response to treatment was defined as a ≥ 30% improvement in score on the scale compared with baseline. Secondary outcomes included changes in scores on the Ashworth Scale and Motricity index, NRS scores for other MS-related symptoms e.g. spasm or sleep quality, Barthel Activities of Daily Living and quality-of-life measures.

In the six-week trial,[6] the difference in improvement in spasticity-symptom scores between Sativex treatment and placebo treatment was statistically significant (difference between groups 0.52 points, 95% CI -1.029 to -0.004, p = 0.048), and significantly more Sativex-treated patients responded to treatment (40% *vs.* 22% for placebo, p = 0.014). There were no significant differences between treatment groups for any of the secondary outcomes.

In the 15-week trial,[7] there were no significant differences between Sativex and placebo for improvements in symptoms, or numbers of patients responding to treatment. There were also no significant differences between groups for any of the other secondary outcomes.

In the two-phase trial,[8] 272 patients (48%) showed a response to treatment during the first four-week, single-blind screening phase, of whom 241 were randomised to the double-blind phase. During the screening phase there was a mean improvement in NRS-spasticity score of 3 points. After 12 weeks' double-blind treatment, spasticity-symptom scores in Sativex-treated patients showed slight improvement (-0.04 points) whilst placebo-treated patients showed slight deterioration (+ 0.81 points). The difference between treatments was statistically significant (difference 0.84 points, 95% CI -1.29 to -0.40, p = 0.0002). Responder analysis showed that 74% of Sativex-treated patients responded to treatment *vs.* 51% of placebo-treated patients (p = 0.0003).

Some secondary outcomes showed significant differences between treatment groups. Compared with placebo, Sativex treatment resulted in greater improvements in spasm frequency and sleep disruption scores (p ≤ 0.005), Barthel Activities of Daily Living (p = 0.0067) and the physicians', patients' and carers' impression of change ratings (p ≤ 0.05).

There were no published trials that compared Sativex with other anti-spasticity medication.

Adverse events

About 1,500 patients have been exposed to Sativex during the clinical trials programme.[1] In the trials reviewed here, about 80% of Sativex-treated patients reported at least one adverse event. The most common adverse events occurring more frequently with Sativex than placebo were: dizziness, fatigue, somnolence, nausea and dry mouth.

Common application-site reactions listed in the Summary of Product Characteristics (SPC) were: oral pain and discomfort, dysgeusia (taste distortion), mouth ulceration and glossodynia (burning sensation in tongue). Regular inspection of the oral mucosa is advised during long-term administration.

Considerations for cost impact and cost-effectiveness

The estimated prevalence of patients with MS in the West Midlands is about 5,000 to 6,000 people (10% of national prevalence[2]). Of those patients an estimated 1,200 will have moderate to severe spasticity.[3]

Costs at current prices from MIMS and the Drug Tariff for a year's treatment with:

- baclofen, 60 mg/day £ 42
- gabapentin 2,400 mg/day £ 429
- Sativex, 6 to 12 sprays/day £2,738 to £5,475
- dantrolene sodium, 225 mg/day £ 554
- diazepam 15 mg/day £ 36
- tizanidine 24 mg/day £ 126

References

1. GW Pharma Ltd. Sativex Oromucosal Spray. SPC. 2010. http://www.medicines.org.uk/EMC/medicine/23262/SPC/Sativex+Oromucosal+Spray/
2. National Collaborating Centre for Chronic Conditions. CG8: Management of multiple sclerosis in primary and secondary care. NICE. 2003. http://www.nice.org.uk/nicemedia/live/10930/29199/29199.pdf
3. Rizzo MA, Hadjimichael OC, Preiningerova J *et al*. Prevalence and treatment of spasticity reported by multiple sclerosis patients. *Mult Scler* 2004;**10:**589-95.
4. Thompson AJ, Toosy AT, Ciccarelli O. Pharmacological management of symptoms in multiple sclerosis: current approaches and future directions. *Lancet Neurol* 2010;**9:**1182-99.
5. National Institute for Health and Clinical Excellence. Sativex as an add-on treatment of moderate to severe spasticity in multiple sclerosis (in progress). NICE. 2010. http://guidance.nice.org.uk/TA/Wave7/34
6. Collin C, Davies P, Mutiboko IK *et al*. Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. *Eur J Neurol* 2007;**14:**290-6.
7. Collin C, Ehler E, Waberzinek G *et al*. A double-blind, randomized, placebo-controlled, parallel-group study of Sativex, in subjects with symptoms of spasticity due to multiple sclerosis. *Neurol Res* 2010;**32:**451-9.
8. Novotna A, Mares J, Ratcliffe S *et al*. A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols (Sativex®), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. *Eur J Neurol* 2011.

Launch date: June 2010 *Manufacturer: GW Pharma* *PL 18024/0009*

WARNING: This sheet should be read in conjunction with the Summary of Product Characteristics

This guidance is based upon the published information available in English at the time the drug was considered. It remains open to review in the event of significant new evidence emerging.

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NICE GUIDANCE ON SATIVEX WAS NOT AVAILABLE AT THE TIME OF ISSUE OF THIS VERDICT

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