Coventry & Warwickshire

Area Prescribing Committee

Drug Positioning Statement	DPS007
Dronabinol/Cannabidiol (Sativex®)▼	October 2013

VERDICT

The Coventry & Warwickshire APC does not recommend the use of Sativex®. The available evidence does not support its use for moderate to severe spasticity in Multiple Sclerosis (MS). Those currently receiving Sativex® should have the option to continue until they and their consultant consider it appropriate to stop.

Specialist Drugs List Status: **Not recommended**

Summary notes

Indication[1]: Sativex® is indicated as treatment for symptom improvement in adult patients with moderate to severe spasticity due to multiple sclerosis (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.

Pharmacological action: Sativex ®contains dronabinol [delta-9-tetrahydrocannabinol, (THC)] and cannabidiol. As part of the human endocannabinoid system (ECS), cannabinoid receptors, CB_1 and CB_2 receptors are found predominantly at nerve terminals where they have a role in retrograde regulation of synaptic function. THC acts as a partial agonist at both CB_1 and CB_2 receptors, mimicking the effects of the endocannabinoids, which may modulate the effects of neurotransmitters (e.g. reduce effects of excitatory neurotransmitters such as glutamate).

Presentation: Oral mucosal spray. Each 100 microlitre spray contains: 2.7 mg delta-9-tetrahydrocannabinol (THC) and 2.5 mg cannabidiol (CBD). Must be kept in the refrigerator between doses.

Dose: A titration period is required to reach the optimal dose (titration table can be found in the summary of product characteristics. Sativex should be sprayed either under the tongue or on to the inside of the cheek and the spray should be directed to a different part of the oromucosa each time it is administered. There should be a 15 minute gap between sprays. In clinical trials, the median number of sprays used per day was 8 (in 2 divided doses).. Doses > 12 sprays per day are not recommended. A 10ml pack size allows delivery after priming of up to 90 sprays of 100microlitres.

Cost comparison (28 day's supply)[2]:

Sativex, 8 sprays per day	£311.00
Baclofen 20mg tds	£3.74
Gabapentin 400mg tds	£4.32

Drug profile

Clinical Effectiveness[3,4,5,6]

In all trials, patients continued existing medications, including anti-spasticity treatment. The primary outcome was a patient rated measure of spasticity, a numerical rating scale (NRS) from 0 (no spasticity or stiffness) to 10 (total spasticity or stiffness). Secondary outcomes included changes in spasm, sleep quality and quality of life measures.

In a six week trial that compared Sativex® with placebo, the difference in improvement in spasticity scores was 0.5 in favour of Sativex® (statistically significant, p=0.048). However, some patients used more than the recommended 12 sprays per day. There were no significant differences for any of the secondary outcomes. There were also no significant differences between groups for secondary outcomes.

In a 15-week trial, some patients took more than the recommended 12 sprays per day. There were no significant differences between Sativex® and placebo for improvements in symptoms or any of the secondary outcomes.

In a two phase study, 572 MS patients with spasticity were enrolled in a 4-week, single-blind treatment period (Phase A), to determine response to Sativex ®.Those patients showing a ≥20% reduction in their spasticity score were classed as Sativex ® responders and suitable to enter the second phase of the trial. 272 patients (48%) were classed as responders. Of these, 241 entered the 12-week, double-blind, Phase B trial, and were randomised to treatment with either Sativex® , up to 12 sprays per day, (n=124) or placebo (n=117). After 12 weeks Sativex® treated patients showed a slight improvement (-0.04 points) whilst placebo treated patients showed a slight deterioration +0.81 points). The difference between treatments is statistically significant (p=0.0002). Some secondary outcomes showed significant differences. The frequency of spasms occurring in the second phase were maintained with Sativex®, but increased by ~2.5/day with placebo[3]. Sleep disturbance worsened in the placebo group (by ~0.6 on the numerical rating scale) but improved in the Sativex® group (by ~0.2) (p<0.0001). The clinical significance of the differences in spasticity and sleep symptoms between placebo and Sativex® is not clear.

In a withdrawal study, 36 patients using Sativex® entered a five-week placebo-controlled, parallel group, randomised withdrawal study. All patients had demonstrated clinically relevant responses to Sativex® whilst on long-term prescription use. After a 7-day baseline period where the subjects continued with Sativex® at their current effective dose level, they ceased Sativex® and were randomised to Sativex® (n=18) or placebo (n=18). They continued with their current effective dose, identified at the start of the baseline period for the next 4 weeks. The primary endpoint was time to treatment failure. Eight Sativex patients (44.4%) and 17 (94%) placebo patients were classed as treatment failures. Sixteen (89%) of placebo patients withdrew vs. 3 (17%) of Sativex patients. Time to treatment failure was significantly in favour of Sativex® (p=0.013).

With long term use, 137 patients continued with Sativex® treatment after a 6 week double-blind and 4 week open-label study. These patients were perceived to have had a benefit from treatment and continued taking it, mimicking clinical practice. 73 of these patients completed at least one year of follow-up. The benefits seen in the primary symptoms (spasticity, spasm, pain and bladder) after the initial 10 weeks were maintained throughout the year.

Safety

Adverse effects[1]**:** Very common (<1 in 10**)** adverse effect: dizziness and fatigue, Common (>1 in 100, <1 in 10) adverse effects include: sore mouth, dry mouth, mouth ulcers, somnolence, nausea, change in appetite, depression, euphoric mood, amnesia, balance disorder, lethargy, vertigo, , No withdrawal syndrome was evident from the small 5 week withdrawal study, but worsening of spasticity symptoms and functional ability were seen with withdrawal of Sativex®.

Elderly[1]**:** Dose is adjusted to individual patient during trial period. The elderly may be more prone to CNS side effects.

Renal & Hepatic Impairment[1]**:** No studies have been carried out in these populations.. Effects may be prolonged. Frequent evaluation by a clinician is recommended.

Cautions/Contra-indications: Caution should be exercised in patients with epilepsy or a history of seizures.

Current place in therapy

National institute for Health and Clinical Excellence (NICE)[7]Clinical guideline 8 for Multiple Sclerosis currently recommends that pharmacological treatment for spasticity associated with MS should initially be with either baclofen or gabapentin. If these are ineffective, or not tolerated, then tizanidine, diazepam, clonazepam or dantrolene should be used. NICE are in the process of reviewing the clinical guideline for multiple sclerosis.

Scottish Medicines Consortium (SMC) [8]

Sativex is not recommended for use within NHS Scotland.

Midlands Therapeutics Review and Advisory Committee (MTRAC) [5]

Sativex ® is not recommended for prescribing as the current evidence for its efficacy and safety is considered to be inadequate to support its use.

Summary

- Not all patients respond to Sativex®. A trial period of four weeks is required. The product license should ensure that Sativex® is only continued in patients who demonstrate a specific minimum level of efficacy following a short term trial of therapy..
- There are few comparisons between Sativex® and placebo. Patients in some trials used more than the recommended dose. It is also not documented if patients were titrated up to maximum tolerated doses of the original anti-spasticity medication before using Sativex®.
- Sativex® has demonstrated efficacy in one large clinical trial (572 patients). Only 42% of patients continued after the first four weeks, the main reason for discontinuation being lack of efficacy. After 12 weeks of treatment, Sativex® responder's had an average improvement in spasticity of 0.84 on an 11 point scale. The clinical significance of this is unclear.
- Limitations of the trials included definitions of disease severity, outcome measures not commonly used in clinical practice, and small effect sizes[5].
- There is limited evidence of efficacy with long term Sativex® treatment. Only 73 of 137 patients completed a one year follow-up after a 10 week trial.
- There are no published trials with active comparators.
- The cost of Sativex® is significantly more than oral anti-spasticity treatments recommended by NICE.
- Sativex® is now placed in Schedule 4 Part I of the Misuse of Drugs Regulations 2001 (as amended) . The legal status of Sativex® may vary between countries, limiting travel.

References

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