New Medicine Assessment

Delta-9-Tetrahydrocannabinol (THC) and Cannabidiol (CBD) (Sativex®)

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

Recommendation: Amber0 – Sativex® is suitable for prescribing in primary care following initiation and dose titration by a specialist. The value of long-term treatment should be re-evaluated periodically by specialist services.

- Little or no specific monitoring required.
- Patient may need a regular review, but this would not exceed that required for other medicines routinely prescribed in primary care.
- Brief prescribing document or information sheet may be required.

Primary care prescribers must be familiar with the drug to take on prescribing responsibility or must get the required information.

Summary of supporting evidence:

- Sativex® provided a statistically significant improvement in patients with MS-related spasticity when compared with placebo over 12 weeks. [6] [9]
- During a four-week study in patients judged to be benefiting from long-term Sativex® therapy, withdrawal of Sativex® caused significantly more patients to report treatment failure than those continuing to receive Sativex®. [7]
- Following unsuccessful management of spasticity with oral medicines, Sativex® is less invasive than alternative interventions (e.g. intrathecal baclofen, intramuscular botulinum toxin).
- There is over 10 years of data relating to the safety profile of Sativex®. Serious adverse events are rare, and the most commonly reported reactions are usually mild to moderate and resolve within a few days even if treatment is continued.
- NICE recommends offering a 4-week trial of Sativex® to treat moderate to severe spasticity in adults with multiple sclerosis when other pharmacological treatments have not been effective.

Date: September 2021

Details of Review

Name of medicine (generic & brand name)**:** Delta-9-Tetrahydrocannabinol (THC) and Cannabidiol (CBD) (Sativex®)

Strength(s) and form(s): 2.7 mg delta-9-tetrahydrocannabinol (THC) and 2.5 mg cannabidiol (CBD) oromucosal spray

Dose and administration:

Titration period:

A titration period is required to reach optimal dose. The number and timing of sprays will vary between patients.

The number of sprays should be increased each day following the pattern given in the table below. The afternoon/evening dose should be taken at any time between 4 pm and bedtime. When the morning dose is introduced, it should be taken at any time between waking and midday. The patient may continue to gradually increase the dose by 1 spray per day, up to a maximum of 12 sprays per day, until they achieve optimum symptom relief. There should be at least a 15-minute gap between sprays.

Day	Number of sprays in the morning	Number of sprays in the evening	(Total number of sprays per day)
1	0	1	1
2	0	1	1
3	0	2	2
4	0	2	2
5	1	2	3
6	1	3	4
7	1	4	5
8	2	4	6
9	2	5	7
10	3	5	8
11	3	6	9
12	4	6	10
13	4	7	11

14	5	7	12

Maintenance period:

Following the titration period, patients are advised to maintain the optimum dose achieved. The median dose in clinical trials for patients with multiple sclerosis is eight sprays per day. Once the optimum dose has been achieved, patients may spread the doses throughout the day according to individual response and tolerability. Re-titration upwards or downwards may be appropriate if there are any changes in the severity of the patient's condition, changes in their concomitant medication or if troublesome adverse reactions develop. Doses of greater than 12 sprays per day are not recommended. [1]

BNF therapeutic class / mode of action:

Cannabinoid/ THC acts as a partial agonist at both cannabinoid receptors (CB1 and CB2 receptors), mimicking the effects of the endocannabinoids, which may modulate the effects of neurotransmitters (e.g. reduce effects of excitatory neurotransmitters such as glutamate).

Licensed indication(s):

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. [1]

Proposed use (if different from, or in addition to, licensed indication above): N/A

Course and cost:

The current list price for Sativex® is £300 for 270 doses. [2] The number of daily sprays required per patient varies on an individual basis. The company reports the median dose in clinical trials to be 8 per day, which would cost around £3,244 per year**.** [3]

Current standard of care/comparator therapies:

- No comparator.

Relevant NICE guidance:

NICE CG186: Multiple sclerosis in adults: management [4]

1.5.19 Consider baclofen or gabapentin as a first-line drug to treat spasticity in MS depending on contraindications and the person's comorbidities and preferences. If the person with MS cannot tolerate one of these drugs consider switching to the other.

1.5.20 Consider a combination of baclofen and gabapentin for people with MS if:

- individual drugs do not provide adequate relief or
- side effects from individual drugs prevent the dose being increased.

1.5.21 Consider tizanidine or dantrolene as a second-line option to treat spasticity in people with MS.

1.5.22 Consider benzodiazepines as a third-line option to treat spasticity in MS and be aware of

their potential benefit in treating nocturnal spasms.

1.5.23 For guidance on THC:CBD spray for treating spasticity in people with MS see the NICE guideline on cannabis-based medicinal products. [amended 2019]

1.5.24 If spasticity cannot be managed with any of the above pharmacological treatments, refer the person to specialist spasticity services.

NICE NG144: Cannabis-based medicinal products [5]

1.3.1 Offer a 4-week trial of THC:CBD spray to treat moderate to severe spasticity in adults with multiple sclerosis, if:

- other pharmacological treatments for spasticity are not effective (see the recommendations on spasticity in NICE's guideline on multiple sclerosis in adults)
- the company provides THC:CBD spray according to its pay-for-responders scheme (it funds the first 3 x10-ml vials if there is agreement for continued funding for people with at least a 20% reduction in spasticity-related symptoms on a 0 to 10 patient-reported numeric rating scale after 4 weeks).

After the 4-week trial, continue THC:CBD spray if the person has had at least a 20% reduction in spasticity-related symptoms on a 0 to 10 patient-reported numeric rating scale.

1.3.2 Treatment with THC:CBD spray should be initiated and supervised by a physician with specialist expertise in treating spasticity due to multiple sclerosis, in line with its marketing authorisation.

Background and context

Multiple sclerosis (MS) is an acquired chronic immune-mediated inflammatory condition of the central nervous system (CNS), affecting both the brain and spinal cord. It affects approximately 100,000 people in the UK. It is the commonest cause of serious physical disability in adults of working age.

People with MS typically develop symptoms in their late 20s, experiencing visual and sensory disturbances, limb weakness, gait problems, and bladder and bowel symptoms. They may initially have partial recovery, but over time develop progressive disability. The most common pattern of disease is relapsing–remitting MS (RRMS) where periods of stability (remission) are followed by episodes when there are exacerbations of symptoms (relapses). About 85 out of 100 people with MS have RRMS at onset. Around two-thirds of people who start with RRMS may develop secondary progressive MS: this occurs when there is a gradual accumulation of disability unrelated to relapses, which become less frequent or stop completely. Also about 10 to 15 out of 100 people with MS have primary progressive MS where symptoms gradually develop and worsen over time from the start, without ever experiencing relapses and remissions. [4]

Spasticity is a common symptom in patients with MS, affecting between 49% and 84% of patients, and impairing quality-of-life. MS-related spasticity is characterised by increased stiffness and slowness in limb movement, development of certain postures, an association with weakness of voluntary muscle power, and with involuntary and sometimes painful spasms of limbs. [3]

NICE guidance recommends that initial pharmacological treatment for spasticity or spasms should be baclofen or gabapentin (unlicensed use). Tizanidine and dantrolene should only be given when treatment with baclofen or gabapentin is unsuccessful or side effects are intolerable. The next pharmacological options for patients with MS-related spasticity unresponsive to simpler treatments are benzodiazepines, intrathecal baclofen or phenol injections (to motor points or intrathecally) or, in specific cases, intramuscular botulinum toxin. [3]

Sativex® is a cannabis-based medicine, containing delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) as an oromucosal spray. Sativex® is licensed for use to improve symptoms of moderate to severe MS related spasticity, in patients who have not responded adequately to other antispasticity medication, in addition to the patient's current anti-spasticity medication. At the November meeting of the LSCMMG it was agreed based on discussions and comments that Sativex for the treatment of spasticity due to MS should be added to the new medicines workplan.

Summary of evidence

Summary of efficacy data in proposed use:

Novotna et al RCT (2011) [6]

This was a randomised, double-blind, placebo-controlled, multicentre, parallel-group, phase III study evaluating the efficacy and safety of Sativex® in adult patients with MS experiencing spasticity of at least moderate severity (defined as a spasticity numeric rating scale [NRS] score of at least 4) not responsive to existing therapies. All patients (n = 572) entered phase A of the study and received Sativex® for four weeks in order to identify patients who responded sufficiently to treatment (≥ 20% improvement from baseline spasticity NRS score). Patients with sufficient response during phase A were eligible to progress to phase B, wherein patients (n = 241) were randomised to receive Sativex® (dose self-titrated through predefined escalation scheme up to a maximum dose of 12 sprays in a 24-hour period; n = 124) or placebo (n = 117) over 12 weeks.

Patients continued to receive their pre-existing MS disease-modifying and/or anti-spasticity medications. The primary endpoint was the change in mean spasticity NRS score from the point of randomisation (entry of phase B) to the last week of treatment. The mean baseline spasticity NRS score in the 572 patients entering phase A was 6.91; of these 272 patients (47.6%) were identified as responders.

In the group of 241 patients entered into phase B, the mean spasticity NRS score at randomisation was 3.90 (3.87 in the Sativex® group and 3.92 in the placebo group). During phase B, this improved by 0.04 in patients receiving Sativex® and worsened by 0.81 in the placebo group; this treatment difference (0.84) was statistically significant (95% confidence interval [CI]: −1.29 to −0.40; p = 0.0002). Similar data was observed during analysis of secondary and tertiary endpoints, with patients who continued to receive Sativex® maintaining responses observed during phase A and patients from the placebo group demonstrating worsened scores; however, the differences did not achieve statistically significance. [3]

Notcutt et al RCT (2012) [7]

This was a placebo-controlled, multicentre, parallel-group, randomised, phase III, withdrawal trial that evaluated the maintenance of efficacy of Sativex® in patients with MS who had gained long-term symptomatic relief from spasticity, and assessed the impact of sudden Sativex® withdrawal in these patients. Eligible patients were those experiencing ongoing benefit from Sativex® for at least 12 weeks prior to study entry (mean duration of Sativex® use: 3.6 years). Patients continued to receive Sativex® at their current effective dose during the seven-day baseline period, and then were randomised to either continue receiving Sativex® or switch to receiving placebo for four weeks. Patients continued to receive their pre-existing MS disease modifying and/or anti-spasticity medications.

Treatment failure occurred in 8/18 (44.4%) patients in the Sativex® group versus 17/18 (94.4%) in the placebo group, and the primary endpoint of time to treatment failure was significantly in favour of Sativex® (median time: > 28.0 days in the Sativex® group versus 1.5 days in the placebo group; hazard ratio: 0.335; CI95%: 0.162 to 0.691; p = 0.013). Most secondary endpoints demonstrated a similar trend, but several, including change in spasticity NRS scores, MAS (modified Ashworth scale measure of spasticity) scores and sleep disruption NRS scores failed to achieve statistical significance. [3]

L Leocani et al RCT (2015) [8]

This prospective, randomized, double-blind, placebo-controlled, crossover study, recruited patients with progressive MS and inadequate response to antispasticity agents. The primary aim of the study was to investigate the effects of Sativex® on neurophysiological measures of spasticity, however clinical assessments of spasticity were studied as a secondary outcome measure. Improvement in the mean lower limb MAS score from baseline to week 4 was significantly greater under treatment with Sativex® than placebo (-21.73 % ± 29.45 vs -5.99 % ± 24.75, p = 0.006). Results for total MAS were similar. The upper limb MAS was negligible at baseline and showed no evident changes after treatment. There was no significant difference in the change from baseline to week 4 in spasticity NRS scores under active vs placebo treatment or in the number of responders (13 vs 10 patients).

J Markova et al RCT (2019) [9]

This was a prospective, randomised, parallel group, double-blind, placebo-controlled two-phase trial in adults with MS and existing moderate to severe spasticity as defined by the NRS scale. Patients received THC:CBD spray as add-on therapy to optimised standard antispasticity medication. Patients up titrated the dosage of THC:CBD spray to a maximum of 12 sprays/day until optimised symptom relief was achieved. Initial responders were identified based on having achieved a minimal clinically important difference (MCID) in MS spasticity. Initial responders at 4 weeks entered a 1- to 4-week washout phase designed to minimise carry-over effects, during

which THC:CBD spray was withdrawn but underlying standard antispasticity treatment was continued. Initial responders whose improvement in the MS spasticity NRS score during Phase A was reduced by ≥80% during the washout period were eligible for Phase B. In Phase B, patients were randomised in a double-blind manner to treatment with THC:CBD spray or placebo for 12 weeks. Patients were advised to re-up-titrate their study medication to the optimal individual dose identified in Phase A, then to maintain the study treatment at this dose while allowing for adjustments according to the patient's needs. Optimisation of underlying antispasticity medications was permitted across all study periods.

The primary efficacy endpoint was the proportion of responders after 12 weeks of randomised treatment in Phase B, where responder was defined as a patient who achieved ≥ 30% improvement (i.e. a clinically important difference [CID]) in the MS spasticity 0–10 NRS score from Phase B baseline. The proportion of responders after 12 weeks of randomised treatment, was significantly higher in the THC:CBD oromucosal spray group (41/53; 77.4%) than in the placebo group (17/53; 32.1%), with an adjusted odds ratio of 7.0 (CI95%: 2.95 to 16.74; p<0.0001; ITT population). At week 4 in Phase B, 81.1% of patients allocated to THC:CBD spray had reached the initial response threshold versus 45.3% in the placebo group (p=0.0007). The mean (SD) number of sprays/day of THC:CBD spray was 7.7 (3.0) at week 4 of Phase A (n=188) and 7.5 (2.6) at week 4 of randomised Phase B (n=102).

Summary of safety data:

According to the Public Assessment Report for Sativex® published by the Medicines and Healthcare Products Regulatory Agency (MHRA) [10], more than 1,800 patients received Sativex® in the clinical trials programme. More than 660 subjects were exposed to Sativex® for more than 6 months and over 310 for more than a year.

In the MS population, the most commonly reported all-causality AEs (in at least 5% of subjects) in order of incidence were dizziness, fatigue, nausea, urinary tract infection, somnolence, vertigo, headache, dry mouth, asthenia and diarrhoea. These events were typically mild or moderate in severity. The full list of adverse events for Sativex® is tabulated below [1]:

	Very Common ≥ 1/10	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1000 to < 1/100**
Infections and infestations			pharyngitis
Metabolism and nutrition disorders		anorexia (including appetite decreased), appetite increased	
Psychiatric disorders		depression, disorientation, dissociation, euphoric mood,	hallucination (unspecified, auditory, visual), illusion, paranoia, suicidal ideation, delusional perception*
Nervous system disorders	dizziness	amnesia, balance disorder, disturbance in attention, dysarthria, dysgeusia, lethargy, memory impairment somnolence	syncope
Eye disorders		vision blurred	
Ear and labyrinth disorders		vertigo	
Cardiac disorders			palpitations, tachycardia
Vascular disorders			hypertension
Respiratory, thoracic and mediastinal disorders			throat irritation
Gastrointestinal disorders		constipation, diarrhoea, dry mouth, glossodynia, mouth ulceration, nausea, oral discomfort, oral pain, vomiting	abdominal pain (upper), oral mucosal discolouration*, oral mucosal disorder, oral mucosal exfoliation*, stomatitis, tooth

			discolouration
General disorders and administration site conditions	fatigue	application site pain, asthenia, feeling abnormal, feeling drunk, malaise	application site irritation
Injury, poisoning and procedural complaints		fall	

Sativex® is contraindicated in:

- patients with hypersensitivity to cannabinoids,
- patients with any known or suspected history or family history of schizophrenia, or other psychotic illness; history of severe personality disorder or other significant psychiatric disorder other than depression associated with their underlying condition,
- breastfeeding.

Use of Sativex® is not recommended in patients with serious cardiovascular disease. Caution should be taken when treating patients with a history of epilepsy, or recurrent seizures. Administration to patients with moderate or severe hepatic impairment is not advised due to the lack of information on the potential for accumulation of THC and CBD with chronic dosing. Frequent clinical evaluation by a clinician is recommended for patients with impaired renal function. Patients who have a history of substance abuse, may be more prone to abuse Sativex as well. [1]

Strengths and limitations of the evidence:

Strengths

- Sativex® provided a statistically significant improvement in patients with MS-related spasticity when compared with placebo over 12 weeks. [6] [9]
- During a four-week study in patients judged to be benefiting from long-term Sativex® therapy, withdrawal of Sativex® caused significantly more patients to report treatment failure than those continuing to receive Sativex®. [7]
- Following unsuccessful management of spasticity with oral medicines, Sativex® is less invasive than alternative interventions (e.g. intrathecal baclofen, intramuscular botulinum toxin).
- There is over 10 years of data relating to the safety profile of Sativex®. Serious adverse events are rare, and the most commonly reported reactions are usually mild to moderate and resolve within a few days even if treatment is continued.
- NICE recommends offering a 4-week trial of Sativex® to treat moderate to severe spasticity in adults with multiple sclerosis when other pharmacological treatments have not been effective.

Limitations

- A key issue considered by MHRA is whether the NRS is a valid measure of spasticity as opposed to a measurement of other symptoms. [10]
- Several RCT trials were split into two phases leading to an enriched selection of patients in phase B who had responded to Sativex® in phase A.
- Sativex® should be directed at different sites on the oromucosal surface, changing the application site each time the product is used, in order to diminish risk of developing application site reactions. There should be at least a 15 minute gap between sprays, so for patients receiving the maximum dose of 12 sprays, administration as per the SPC dosing pattern would take a minimum of 90 minutes for the seven evening doses and 60 minutes for the five morning doses. [3]

- Patients report that Sativex® has an unpleasant taste.

Summary of evidence on cost effectiveness:

A cost-utility analysis (CUA) of Sativex® as an add-on to standard of care treatment (SoC) in its licensed indication, versus SoC, where SoC is defined as a combination of anti-spasticity medication and physical therapies was submitted to the AWMSG.

The base results of the CUA are tabulated below:

Table 1. Base case CUA results

	SoC	SoC plus Sativex®	Difference	ICER	Key plausibility considerations
Total cost (per patient)	£98,501	£102,337	£3,836	£10,891	The model does not address the decision problem of Sativex® plus SoC versus SoC alone, as the costs and benefits of Sativex® over the first cycle is included in the SoC alone arm. Short-term data are modelled to 30 years, which is subject to uncertainty. The assumed dose of Sativex® in the model is lower than observed in the key trials.
Total QALY (per patient)	10.65	11.00	0.35		

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year; SoC: standard of care.

The company also provided supplementary analyses to explore the combined impact of a shorter time horizon of analysis of five years together with the inclusion of home care visits in the model, and a range of alternative Sativex® dose assumptions that span the doses observed in a trial of Sativex® [6] (but retaining the assumption of Sativex® costs and benefits for the first four weeks in the SoC alone arm). In each of these analyses, the inclusion of home care costs outweighs the additional costs of Sativex® to the extent that Sativex® plus SoC dominates SoC alone (i.e. Sativex® plus SoC is less costly and more effective than SoC alone).

Table2. Base case CUA results

Scenario Description	Scenario details	Incremental cost per QALY	Plausibility considerations
Inclusion of carer costs	As base case but with inclusion of home carer costs; estimates based on expert survey	Sativex® dominant over SoC (cost saving of £33,609 and gain of 0.35 QALYs)	Incorporation of home carer costs may be relevant if these are considered to fall into the category of NHS and Personal Social Services costs. This result is driven by the extrapolation of 16-week data over 30 years, which leads to a higher proportion of patients on SoC modelled to require home care visits over time.
Exclusion of equipment costs	As base case but with exclusion of equipment costs	£11,929 (Additional cost of £4,202 and gain of 0.35 QALYs)	Demonstrates that equipment cost offsets are not a major driver of the base case analysis.
Exclusion of spasticity worsening	As base case but with removal of assumption spasticity worsens in all patients over time	£6,829 (Additional cost of £3,336 and gain of 0.49 QALYs)	Seems plausible that patients would deteriorate over time, although MS can relapse and remit over time. It is unclear whether this or the base case analysis approach is most plausible, because the base case analysis would mean that at 30 years, 30% of the cohort has died and 86% of the remaining patients have the most severe levels of spasticity possible, which seems unlikely
Discontinuation of Sativex® to same health state	As base case but assumes that when patients discontinue Sativex® they maintain the treatment benefit they had received	£4,364 (Additional cost of £2,019 and gain of 0.46 QALYs)	This scenario would appear to bias the analyses in favour of Sativex®. Trial data demonstrate that patients who responded to Sativex® deteriorated when it was discontinued. Assumption of base case analysis would seem more plausible in this regard.
Discount rates sensitivity	As base case but with discount rate on costs and benefits varied together in range 0%–6% per annum	£10,665–£11,051	Model is not sensitive to assumed discount rate.
MS: multiple sclerosis; QALY: quality-adjusted life-year; SoC: standard of care.			

N.B. The list price of Sativex® was higher at the time of publication of the AWMSG advice and submission of the CUA.

Prescribing and risk management issues:

Treatment must be initiated and supervised by a physician with specialist expertise in treating this patient population.

The spray container should be shaken before use and the spray should be directed at different sites on the oromucosal surface changing the application site each time the product is used.

Patients should be advised that it might take up to 2 weeks to find the optimal dose and that undesirable effects can occur during this time, most commonly dizziness. These undesirable effects are usually mild and resolve in a few days. However, physicians should consider maintaining the current dose, reducing the dose or interrupting, at least temporarily, the treatment depending on seriousness and intensity.

To minimise variability of bioavailability in the individual patient, administration of Sativex® should be standardised as far as possible in relation to food intake. In addition, starting or stopping some concomitant medicinal products may require a new dose titration.

The patient's response to Sativex® should be reviewed after four weeks of treatment. If a clinically significant improvement in spasticity related symptoms is not seen during this initial trial of therapy, then treatment should be stopped. [1]

Commissioning considerations:

Innovation, need and equity implications of the intervention:

Currently available treatment for spasticity is limited and spasticity continues to cause substantial disability in a cohort of patients with troublesome spasticity despite maximal therapy with other established agents. There is, therefore, an unmet clinical need in this cohort of patients. [10]

Financial implications of the intervention:

Assuming a prevalence for MS of 190 cases per 100,000 of population as defined by analysis published by Public Health England [11], there are an estimated 3,325 cases of MS in Lancashire and South Cumbria. AWMSG used the assumptions that 34% of MS patients had moderate or severe spasticity, 45.9% had used more than two oral medicines to treat spasticity, and that 50% of these patients would be uncontrolled and eligible for Sativex® treatment. This equates to an estimated 260 eligible patients in Lancashire and South Cumbria.

The total annual acquisition cost of treating all eligible patients with Sativex® assuming the number of sprays used matches the median number of sprays used in clinical trials is:

260 X £3,244 = **£843,440**

NB. This cost does not take into account any potential savings which may arise as a result of reduced care costs compared to standard care as detailed in the CUA submitted to the AWMSG.

Service Impact Issues Identified:

Sativex® has a Red RAG status in Lancashire and South Cumbria with the majority of prescribing occurring via specialist services at Lancashire Teaching Hospitals. Altering the RAG status to enable prescribing in primary care is not expected to create any service impact above and beyond that expected for other Green/Amber0 medicines supplied in primary care. There is no specific monitoring required for Sativex® outlined in the SPC, however it would be anticipated that specialist services would advise primary care if any monitoring is necessary e.g. in renal or hepatic impairment.

Equality and Inclusion Issues Identified:

See Attached

Cross Border Issues Identified:

Pan Mersey APC have an Amber “patient retained by specialist” RAG for Sativex®. This allows prescribing in primary care following specialist recommendation. The patient is not discharged from specialist care.

GMMG do not have a position outlined for Sativex®.

Legal Issues Identified:

N/A

Media/ Public Interest:

N/A

References

[1] Electronic Medicines Compendium, "Summary of Product Characteristics," GW Pharma Ltd, June 2010. [Online]. [Accessed May 2021].

[2] Business Services Authority, "NHS Electronic Drug Tariff," May 2021. [Online]. Available: https://www.drugtariff.nhsbsa.nhs.uk/#/00803325-DC/DC00803319/Home. [Accessed May 2021].

[3] All Wales Medicines Strategy Group, "AWMSG Secretariat Assessment Report: Delta-9-tetrahydrocannabinol/cannabidiol (Sativex®) 2.7 mg/2.5 mg oromucosal spray," July 2014. [Online]. Available: https://awmsg.nhs.wales/files/appraisals-asar-far/awmsg-secretariat-appraisal-report-asar-delta-9-tetrahydrocannabinol-cannabidiol-sativex-644/. [Accessed May 2021].

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[6] A Novotna 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 casued by multiple sclerosis," *Eur J Neurol,* vol. 18, no. 9, pp. 1122-31, 2011.

[7] W Notcutt et al, "A placebo-controlled, parallel-group, randomized withdrawal study of subjects with symptoms of spasticity due to multiple sclerosis who are receiving long-term Sativex (nabiximols)," *Mult Scler,* vol. 18, no. 2, pp. 219-228, 2012.

[8] L Leocani et al, "Sativex and clinical-neurophysiological measures of spasticity in progressive multiple sclerosis," *J Neurol,* vol. 262, pp. 2520-2527, 2015.

[9] J Markova et al, "Sativex as add-on therapy vs. further optimized first-line ANTispastics (SAVANT) in resistant multiple sclerosis spasticity: a double-blind, placebo-controlled randomised clinical trial," *International Journal of Neuroscience,* vol. 129, no. 2, pp. 119-128, 2019.

[10] Medicines and Healthcare Products Regulatory Agency, "Public Assessment Report Sativex Oromucosal Spray UK/H/2462/001/DC," United Kingdom, 2010.

[11] Public Health England, "Multiple sclerosis: prevalence, incidence and smoking status - data briefing," February 2020. [Online]. Available: https://www.gov.uk/government/publications/multiple-sclerosis-prevalence-incidence-and-smoking-status/multiple-sclerosis-prevalence-incidence-and-smoking-status-data-briefing#:~:text=The%20estimate%20for%20the%20prevalence,cases%20per%20100%2C000%20popula. [Accessed May 2021].

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality