Surrey Heartlands Integrated Care System Area Prescribing Committee (APC)

Integrated Care Partnerships (ICPs) (Surrey Downs, Guildford & Waverley, North West Surrey, East Surrey (as part of the CRESH system) & associated partner organisations.

Evidence review for Area Prescribing Committee (APC)

Medicine details	
Name, brand name	Medicinal Cannabis delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) (Sativex Oromucosal Spray®) Schedule 4 Part 1 (CD Benz POM)
Manufacturer	GW Pharma Ltd
Proposed indication	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. *Author's note: Spasticity refers to feelings of stiffness and a wide range of involuntary muscle spasms (sustained muscle contractions or sudden movements).*
Requested by	Dr David Barnes Consultant Neurologist Ashford and St Peter's Honorary Senior Lecturer at St George's

SUMMARY

Clinical Effectiveness and Safety

As described in the following NICE guidelines –

1. Multiple sclerosis in adults: management clinical guideline CG186
   Published: October 2014 Last updated: November 2019
2. Cannabis-based medicinal products NICE guideline NG144
   Published: November 2019 Last updated: March 2021

NICE published a clinical guideline NG144- Cannabis-based medicinal products in November 2019. The NICE committee for NG144 made the following recommendations:

- 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)

- T*he manufacturer will provide the first 3 x 10ml vials of Sativex® 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 four weeks.*
  This means that the manufacturer covers the cost of the first pack of Sativex® (3 x 10ml vials) for the purposes of trialling patients to assess their response to the medicine, with a commitment that prescribing continues should they meet the response threshold set out above.

The committee noted that *'that the evidence showed benefits of THC:CBD spray (licensed product in UK: Sativex®) for treating spasticity in people with multiple sclerosis. There were reductions in some measures of patient-reported spasticity and no difference in adverse events in the treatment or placebo groups, although much of the evidence was assessed as low quality.*

The committee agreed that the longer-term benefits of THC:CBD spray are likely to outweigh any potential harms, although it was not clear how benefits related to improvements in quality of life.'

These recommendations were a change to NICE's previous guidance on treating spasticity in adults with multiple sclerosis, which did not support the use of THC:CBD spray (Sativex®). NICE expect the changes in recommendation will lead to THC:CBD spray being used as an add-on treatment for adults with treatment-resistant spasticity due to multiple sclerosis, with concomitant reductions in the need for supportive care.
With respect to prescribing, NICE noted the following:
'Based on current legislation, the complexity of the conditions, and the licensed (nabilone and Sativex®) and unlicensed status of these medicines, the committee agreed that the initial prescription of unlicensed cannabis-based medicinal products must be made by a specialist medical practitioner (a doctor included in the register of specialist medical practitioners [the Specialist Register]). They should also have a special interest in the condition being treated. The committee also agreed that THC:CBD spray should be initiated by a physician with special expertise in treating spasticity due to multiple sclerosis.'
'The committee discussed whether shared care would be appropriate and in the patient's best interest. They agreed that a shared care agreement could be considered, which could involve other healthcare professionals such as GPs and non-medical prescribers if they were confident to take on the responsibility of prescribing.'
'The committee agreed that after the initial assessment and prescription by a specialist, allowing other prescribers to prescribe cannabis-based products under specialist direction would improve access for patients.'

Patient factors

1. Spasticity is a very common and disabling manifestation of multiple sclerosis. Management is made difficult by dose-dependent side effects and limited efficacy of existing therapies in some patients. Sativex® offers a novel, effective and relatively safe addition to our options for treatment.
2. Also, it is a simple oral spray, and does not require swallowing which may be impaired in some patients.

Cost implications

Cost:

Drug Tariff price is £300 per bottle (November 2021)

Each bottle has 270 doses

Median daily dose is 8 sprays (according to SPC) therefore lasting 33 days.

Approx 11 bottles a year costing £3300 per patient per year

What are the costs of comparative treatments?
Baclofen and Diazepam are about £50 per annum (variable dose) and Tizanidine is around £730 per annum (based on average dosage and BNF cost in November 2021)
These are not alternatives to Sativex® but used in the pathway ahead of it.

What is population cost per 100,000 population?

NICE Cannabis-based medicinal products (NG144)	**NICE assumption**	**Number of people**
Assumptions for an **adult** population		100,000
Prevalence of multiple sclerosis (MS)*	0.21%	210
Proportion of adults reporting spasticity-related symptoms	60%	126
Proportion of adults with spasticity-related symptoms which are rated as moderate or severe	44.5%	56
Proportion of adults eligible for treatment with THC:CBD spray due to other drug treatments not being effective	20%	11
Proportion of people who experience at least a 20% reduction in spasticity symptoms on a 0 to 10 patient-reported numeric rating scale after 4 weeks of treatment	75.2%	8.4

*NICE CG 186 data on the prevalence of MS is affects approximately 100,000 people in the UK (pop^{n} 68,362,503). Local estimates are 100 to 120 in 100,000 (Health and social care needs assessment, Frail older people in North West Surrey CCG)

A MS prevalence of 0.146% (based on NICE CG186 prevalence, mid-way between local and NICE NG144 estimates) was used in the calculations for Place in the NICE resource impact tool.

Place	Surrey Downs	East Surrey	Guildford and Waverley	North West Surrey
Total resource impact - year 4 onwards	£28,130	£17,743	£20,513	£33,593

Locally there are 10 people requiring Sativex® in ASPH.

Are there additional health costs related to use of the medicine?
No

Are there any savings from using the medicine?
No realisable savings.
Potentially reduced hospital admissions due to spasticity complications.
Potentially reduced primary care contacts due to complications of spasticity.

Is there any cost-effectiveness data? See NICE NG144 in which they considered results from a new economic model developed specifically for the cannabis guideline. The model included data from all relevant trials, longer-term registry data and data on adverse events. In reflection of the trial evidence, the model predicted that the average person would receive a quality of life (QALY) gain equivalent to around 30 days perfect health with THC:CBD spray added to standard care. The acquisition costs of the treatment are offset by predicted savings in management costs. The model estimates that THC:CBD spray would offer sufficient QALY gains if reduction in spasticity led to a halving of management costs and the acquisition cost of THC:CBD spray was also reduced (in addition to the existing pay-for-responders scheme). The committee agreed that under these conditions THC:CBD spray could be recommended to treat moderate to severe spasticity in adults with multiple sclerosis if other pharmacological treatments had not been effective.

Pay for responders Scheme
As outlined in NICE and highlighted in a letter from Keith Ridge (Chief Pharmaceutical Officer NHS England and NHS Improvement) in September 2021 – letter attached.
The manufacturer will provide the first 3 x 10ml vials of Sativex® 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 four weeks.
This means that the manufacturer covers the cost of the first pack of Sativex® (3 x 10ml vials) for the purposes of trialling patients to assess their response to the medicine, with a commitment that prescribing continues should they meet the response threshold set out above.

Relevant guidance / reviews

NICE Guidance NG144
1.3 Spasticity
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[2].

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

Local guidelines

North Central London (NCL)	AMBER shared care
Sussex Area Prescribing Committee	AMBER shared care

Likely place in therapy relative to current treatments

FROM NICE Multiple sclerosis in adults: management Clinical guideline [CG186]

Spasticity

1.5.16 In people with MS assess and offer treatment for factors that may aggravate spasticity such as constipation, urinary tract or other infections, inappropriately fitted mobility aids, pressure ulcers, posture and pain.

1.5.17 Encourage people with MS to manage their own spasticity symptoms by explaining how doses of drugs can be adjusted within agreed limits.

1.5.18 Ensure that the person with MS: has

- tried the drug at an optimal dose, or the maximum dose they can tolerate
- stops the drug if there is no benefit at the maximum tolerated dose (but note any special precautions needed when stopping specific drugs)
- has their drug treatment reviewed at least annually once the optimal dose has been reached.

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.

1.5.20Consider 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.

See the summary of product characteristics for gabapentin and baclofen and the British National Formulary , and use caution when using these drugs in combination. In October 2014, this was an off-label use of gabapentin. See NICE's information on prescribing medicines and the 2019 Drug Safety Update from the MHRA .

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.

Local specialists advice

Gabapentin and dantrolene are not routinely used in MS centres locally. Baclofen and tizanidine are the preferred alternatives. Sativex® would be used 4th line after baclofen, tizanidine and a benzodiazepine.

Recommendation to APC

To add as a fourth line option where other pre-existing drug treatments (first, second and third line as above) have been ineffective, poorly tolerated or not clinically appropriate, for symptom improvement in adult patients with moderate to severe spasticity due to multiple sclerosis (MS). Initiated and supervised by a consultant neurologist with specialist expertise in MS.

Continue if the person has had at least a 20% reduction in spasticity-related symptoms on a 0 to 10 patient-reported numeric rating scale after a 4-week trial.
The maintenance dose must be established by the initiating consultant neurologist.

Suitable for transfer of care to GP **BLUE** (no additional monitoring required)
After maintenance dose established, prescribing may transfer to GP.
Minimum 8 weeks specialist prescribing. 4 weeks initiation and at least 4 week maintenance.

Medicine details	
Name and brand name	Medicinal Cannabis delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) (Sativex Oromucosal Spray®)
Licensed indication, formulation and usual dosage	FROM SPC 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. 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. The patient may gradually increase the dose by 1 spray per day, up to a maximum of 12 sprays per day, until they achieve optimum symptom relief.
Summary of mechanism of action, and relevant pharmacokinetics	FROM SPC As part of the human endocannabinoid system (ECS), cannabinoid receptors, CB1 and CB2 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 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). In animal models of MS and spasticity CB receptor agonists have been shown to ameliorate limb stiffness and improve motor function. These effects are prevented by CB antagonists, and CB1 knockout mice show more severe spasticity. In the CREAE (chronic relapsing experimental autoimmune encephalomyelitis) mouse model, Sativex® produced a dose-related reduction in the hind limb stiffness.
Safety	FROM SPC The Sativex® clinical program has so far involved over 1500 patients with MS in placebo-controlled trials and long-term open label studies in which some patients used up to 48 sprays per day. The most commonly reported adverse reactions in the first four weeks of exposure were dizziness, which occurs mainly during the initial titration period, and fatigue. These reactions are usually mild to moderate and resolve within a few days even if treatment is continued. When the recommended dose titration schedule was used, the incidence of dizziness and fatigue in the first four weeks was much reduced. Link to SPC
Important drug interactions	FROM SPC Co-administration of Sativex® with other CYP3A4 substrates may result in an increase in plasma concentration of the concomitant drug. A review of the dosing regimen of such medication is advised.

	The two main components of Sativex®, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are metabolised by the cytochrome P-450 enzyme system. Link to SPC for details General Care should be taken with hypnotics, sedatives and drugs with potential sedating effects as there may be an additive effect on sedation and muscle relaxing effects. Although there has been no greater rate of adverse events in patients already taking anti-spasticity agents with Sativex®, care should be taken when co-administering Sativex® with such agents since a reduction in muscle tone and power may occur, leading to a greater risk of falls. Sativex® may interact with alcohol, affecting co-ordination, concentration and ability to respond quickly. In general, alcoholic beverages should be avoided whilst using Sativex®, especially at the beginning of treatment or when changing dose. Patients should be advised that if they do drink alcohol while using Sativex® the additive CNS effects may impair their ability to drive or use machines, and increase the risk of falls. Hormonal contraceptives Sativex® has been observed to induce drug metabolizing enzymes and transporters in vitro. Sativex® may reduce the effectiveness of systemically acting hormonal contraceptives, and therefore women using systemically acting hormonal contraceptives should add an additional second barrier method.
Monitoring requirements	As per existing drug treatments, monitoring of treatment response by specific symptoms and monitoring side effects to ensure medication is tolerated. **No drug specific monitoring requirements**
Prescribing considerations	• Likely traffic light status (see attached guidelines) Colour classification guidelines Sativex® is included in the Misuse of Drugs Regulations 2001 in the Schedule 4 (CD Benz) category which means that: *Schedule 4 includes in Part I drugs that are subject to minimal control, such as benzodiazepines, non-benzodiazepine hypnotics and Sativex®. Controlled drug prescription requirements do not apply and Schedule 4 Controlled Drugs are not subject to safe custody requirements. Records in registers do not need to be kept (except in the case of Sativex®).* To add as a fourth line option where other pre-existing drug treatments (baclofen/gabapentin, tizanidine/dantrolene, a benzodiazepine) have been ineffective, poorly tolerated or not clinically appropriate, in the treatment of multiple sclerosis. Initiated and supervised by a consultant neurologist with specialist expertise in MS. Suitable for transfer of care to GP BLUE (no additional monitoring) Note: Tizanidine which is used ahead of Sativex® was agreed as a BLUE traffic light status in September 2018. There is not additional monitoring for Sativex® The initial 4 week trial to assess response must be initiated by a specialist (patient must have at least a 20% reduction in spasticity-related symptoms on a 0 to 10 patient-reported numeric rating scale as per NICE guidelines NG144)

	Thereafter if there is an adequate response, the patient will continue treatment for long term until a change in function. The initial maintenance dose must be prescribed by the initiating specialist. After maintenance dose established, prescribing may transfer to GP. Minimum 8 weeks specialist prescribing
Other considerations	All Sativex® prescribing will be in line with SPC, BNF and NICE guidance therefore a local information sheet has not been prepared in advance of the APC meeting.

Potential patient group (if appropriate to include)	
Brief description of disease	From NICE Multiple sclerosis (MS) affects the way nerve cells carry messages around the body. 'Sclerosis' means 'scarring', and in MS the coating around the nerves becomes scarred, affecting how the body functions. MS causes scarring at 'multiple' (many) places in the nervous system causing different symptoms. People with MS tend to have their first symptoms before they are 50. Spasticity refers to feelings of stiffness and a wide range of involuntary muscle spasms (sustained muscle contractions or sudden movements). It is one of the more common symptoms of MS. Spasticity may be as mild as the feeling of tightness of muscles or may be so severe as to produce painful, uncontrollable spasms of extremities, usually of the legs. Spasticity may also produce feelings of pain or tightness in and around joints and can cause low back pain. Although spasticity can occur in any limb, it is much more common in the legs. A cure for MS hasn't yet been found. Some treatments can slow down some types of MS, and these are covered in other NICE guidance. There are also lots of different ways to manage MS symptoms.
Potential patient numbers per 100,000	St Peters Hospital estimate 10 to 15 people per year NICE resource impact template suggests 8 people per 100,000 adult population may be eligible
Outcomes required	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. Patient-reported outcome (PRO) scale

Summary of current treatment pathway

See NICE Guidance below

Evidence review

NICE Multiple sclerosis in adults: management
Clinical guideline [CG186] 08 October 2014 Last updated: November 2019
1.5 MS symptom management and rehabilitation
Spasticity
1.5.16 In people with MS assess and offer treatment for factors that may aggravate spasticity such as constipation, urinary tract or other infections, inappropriately fitted mobility aids, pressure ulcers, posture and pain.

1.5.17 Encourage people with MS to manage their own spasticity symptoms by explaining how doses of drugs can be adjusted within agreed limits.

1.5.18 Ensure that the person with MS:

- has tried the drug at an optimal dose, or the maximum dose they can tolerate
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- has their drug treatment reviewed at least annually once the optimal dose has been reached.

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

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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 guideline [NG144] Cannabis-based medicinal products
Published: November 2019 Last updated: March 2021
Recommendations

1.3 Spasticity
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.

Equity / Stakeholder views (if relevant)	
Decisions of local Trusts DTCs and neighbouring APCs	1. The North Central London (NCL) Shared Care Group recently (Dec 2020) informed us of a change in their formulary status of Sativex® for the treatment of multiple sclerosis related spasticity by the tertiary service at The National Hospital for Neurology and Neurosurgery (NHNN). The change in formulary status now allows for continuation of prescribing by GPs under a shared care protocol following specialist initiation in line with NICE guidance. NCL shared care document attached 2. Sussex Health and Care Partnership September 2021 Agreed Sativex® as an Amber Shared care medicine. Document attached
Recommendations from national / regional decision making groups	NICE guidance – see above RMOC shared care guidance - RMOC have published a standard approach to shared care for medicines, this guidance describes characteristics of medicines requiring shared care as a medicine which requires frequent monitoring which can be undertaken in the primary care setting, but is such that overarching specialist involvement is retained. Sativex® does not require frequent monitoring however the condition does. Local clinicians would like to keep prescribing within the hospital at least initially.
Stakeholder views	Removed for PAD upload
CCG priorities	

Health economic considerations	
Cost per year per patient	Include annual cost per patient, and population cost per 100,000 people **See above cost implications section**
Alternative treatments cost per patient per year	Alternative therapies will have been tried before this therapy
Other financial considerations (if relevant)	
Health economic data (if available)	

Attachments
1. Letter from Keith Ridge - Prescribing of THC:CBD spray (Sativex®) in line with NICE NG144 2. North Central London, Joint Formulary Committee, Shared Care Guideline Sativex® Treatment of Multiple Sclerosis related Spasticity 3. Sussex Health and Care Partnership – Shared Care Protocol - Sativex® for a selected cohort of adults with moderate to severe spasticity with Multiple Sclerosis

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Declaration of Interest:

None

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09/11/2021

Declaration of Interest:

Nil