New Medicine Assessment

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

For Refractory Neuropathic Pain

Recommendation: Black

Delta-9-Tetrahydrocannabinol (THC) and Cannabidiol (CBD) (Sativex®) is not recommended for NHS use in Lancashire and South Cumbria.

Summary of supporting evidence:

- There is a small group of patients with refractory chronic neuropathic pain and neurological conditions who have been unresponsive to four or more medicines or have been unable to gain adequate relief from non-pharmacological treatments.
- A Cochrane Review found there was low/moderate quality evidence demonstrating the effectiveness of cannabis-based medicines in the treatment of chronic neuropathic pain.
- The Cochrane review failed to find any high-quality evidence for the effectiveness of medicinal-cannabis for the management of chronic neuropathic pain. This may stem from the difficulties in conducting clinical trials in disabled patients with rare conditions.
- A report produced for the Canadian health service concluded that the evidence suggests some benefit for medicinal-cannabis in the management of chronic neuropathic pain.
- The Canadian report also noted consensus guidelines advocating the use of medicinal-cannabis at specific points in the treatment pathway for chronic neuropathic pain.
- An audit of practice in a local trust which is responsible for the majority of Sativex® prescribing indicated that improvements in neuropathic pain symptoms were more commonly reported than improvements in any other symptoms.
- The use of Sativex® for the management of chronic neuropathic pain is unlicensed and there is a lack of consensus guidance in the UK.
- Sativex® is significantly more expensive that the alternative pharmacological treatments for the management of refractory neuropathic pain.

Date: October 2022

Details of Review

Name of medicine (generic & brand name)**:**

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

Strength(s) and form(s):

Oromucosal Spray. Each single100 microlitre spray contains:

2.7 mg delta-9-tetrahydrocannabinol (THC) and 2.5 mg cannabidiol (CBD) from *Cannabis sativa L*.

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.

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

Unlicensed indication - Refractory Neuropathic Pain.

Course and cost:

The current (September 2022) drug tariff list price for Sativex® is £300 for 270 doses. The number of daily sprays required per patient varies on an individual basis. Based on the available published clinical studies and local feedback doses used in refractory neuropathic pain exceed those used for moderate to severe spasticity in MS. Studies included in a Cochrane Review indicate the use of up to 48 sprays in 24 hours. [2]

The company reports the median dose in clinical trials for the licensed use as 8 sprays per day, which would cost around £3,244 per year

If used at maximal dose of 48 sprays observed in neuropathic pain trials, the cost would rise to £19,464.

Local audit data suggests an average dose of 7 sprays daily which would lead to a cost of £2,838.

Current standard of care/comparator therapies:

- THC:CBD spray is likely to be prescribed when all other pharmacological treatments have been exhausted and patients are still experiencing refractory symptoms.

- The LSCMMG recommends nortriptyline as a 3rd line treatment for chronic neuropathic pain.

  Nortriptyline 10 mg tablets = £2.24/ 100 tablets
  Nortriptyline 25 mg tablets = £2.46 / 100 tablets
  At minimum dose of 10 mg daily, monthly cost / patient = 28 x £0.08 = £0.63
  At maximum dose of 75 mg daily, monthly cost / patient = 84 x £0.26 = £2.07 (3x 25 mg tablets).
  Based on the September 2022 Drug Tariff list price.

Relevant NICE guidance:

Neuropathic pain in adults: pharmacological management in non-specialist settings: CG173

Treatments that should not be used

1.1.12 Do not start the following to treat neuropathic pain in non-specialist settings, unless advised by a specialist to do so:

- cannabis sativa extract [3]

Cannabis-based medicinal products: NG144

1.2 Chronic pain

1.2.1 Do not offer the following to manage chronic pain in adults:

- nabilone
- dronabinol
- THC (delta-9-tetrahydrocannabinol)
- a combination of cannabidiol (CBD) with THC.

1.2.2 Do not offer CBD to manage chronic pain in adults unless as part of a clinical trial.

1.2.3 Adults who started cannabis-based medicinal products to manage chronic pain in the NHS before this guidance was published (November 2019) should be able to continue treatment until they and their NHS clinician think it appropriate to stop. [4]

Background and context

Neuropathic pain is very challenging to manage because of the heterogeneity of its aetiologies, symptoms and underlying mechanisms. There is often uncertainty regarding the nature and exact location of a lesion or health condition associated with neuropathic pain, particularly in non-specialist settings. Examples of common conditions that have peripheral neuropathic pain as a symptom are painful diabetic neuropathy, post-herpetic neuralgia, trigeminal neuralgia, post-surgical chronic neuropathic pain, and neuropathic cancer pain (such as, chemotherapy-induced neuropathy, neuropathy secondary to tumour antigens, or caused by direct invasion or compression of neural structures). Examples of conditions that can cause central neuropathic pain include stroke, spinal cord injury and multiple sclerosis. Neuropathic pain can be intermittent or constant, and spontaneous or provoked. Typical descriptions of the pain include terms such as shooting, stabbing, like an electric shock, burning, tingling, tight, numb, prickling, itching and a sensation of pins and needles. People may also describe symptoms of allodynia (pain caused by a stimulus that does not normally provoke pain), hyperalgesia (an increased response to a stimulus that is normally painful), anaesthesia dolorosa (pain felt in an anaesthetic [numb] area or region), and sensory gain or loss. [3]

The current NICE guidance for the pharmacological management of neuropathic pain suggests offering a choice of amitriptyline, duloxetine, gabapentin, or pregabalin as initial treatment for neuropathic pain (except for trigeminal neuralgia), with switching if the first, second, or third drugs tried are not effective or not tolerated. There is a need to explore other treatment options, with different mechanisms of action and from different drug categories, for treatment of neuropathic pain syndromes. Medical cannabis has been promoted by some patient organisations and advocates for the treatment of chronic pain refractory to conventional treatment and is available for pain management in some countries of the world, e.g. Canada and Israel. [2]

Sativex® is a solution for oromucosal use containing a combination of two extracts from Cannabis sativa L., delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC acts as a partial agonist of cannabinoid (CB) receptors, CB1 and CB2 receptors, which are found predominantly at nerve terminals where they have a role in retrograde regulation of synaptic function. It may modulate the effects of neurotransmitters. Sativex® for the management of refractory neuropathic pain was prioritised following a request from Lancashire Teaching Hospitals. The clinician requested that Sativex be considered in patients with refractory neuropathic pain in neurological conditions regardless of whether a patient has concomitant spasticity.

Summary of evidence

Summary of efficacy data in proposed use:

THC:CBD spray is already approved for use in Lancashire and South Cumbria 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.

The evidence in this review focusses on the use of THC:CBD spray for refractory neuropathic pain in:

- Non-MS patients
- MS patients without moderate/severe spasticity which is unresponsive to anti-spasticity medication.

This evidence review is separated into evidence included in the Cochrane review of cannabis medicinal products in chronic neuropathic pain, and evidence published after the Cochrane

review.

Cochrane Review M Mucke et al 2018 [2]

The review included 16 studies, 2 to 26 weeks long, with 1750 participants. All studies compared cannabis-based medicines with placebo except one study that compared synthetic THC with dihydrocodeine (DHC). Studies compared an oromucosal spray with a plant-derived combination of THC and CBD (10 studies), inhaled herbal cannabis (two studies), synthetic THC (nabilone) (two studies) and plant-derived THC (dronabinol) (two studies).

All cannabis-based medicines (at any dose) pooled together were superior to placebo for substantial (50% and more) (low-quality evidence) and moderate (30% and more) pain relief (moderate-quality evidence), for global improvement (very low-quality evidence), and in reduction of mean pain intensity (low-quality evidence), sleep problems (low-quality evidence), and psychological distress (low-quality evidence). The effect sizes of mean pain intensity, sleep problems and psychological distress were clinically relevant. There was moderate-quality evidence that more people dropped out due to adverse events with cannabis-based medicines compared to placebo. There was low-quality evidence that more people reported any adverse event and adverse events of the central nervous system and psychiatric disorders with all cannabis-based medicines pooled together than with placebo. The effect size of adverse events of the nervous system disorders was clinically relevant. There was no difference between all cannabis-based medicines pooled together and placebo in the frequency of serious adverse events (low-quality evidence), for improvement of health-related quality of life (low-quality evidence) and dropouts due to lack of efficacy (moderate-quality evidence).

There was no high-quality evidence suggesting that any cannabis-based medicine (herbal cannabis, THC/CBD oromucosal spray, synthetic or plant-based THC) was of value in treating people with chronic neuropathic pain.

Characteristics of participants of studies included in the Cochrane Review

Of the 16 studies included the Cochrane Review, five studies were with MS (or defected neurological function in the case of one study), three studies with neuropathic pain in patients with diabetic polyneuropathy, three studies with mixed peripheral pain of various aetiologies, one study with spinal cord injury, one study with HIV neuropathy, one study with chemotherapy-induced polyneuropathy, and one study with mixed central or peripheral pain of various aetiologies.

The efficacy of cannabis-based medicines for treating refractory neuropathic pain in patients with neurological conditions is of particular interest to the clinician who requested this new medicine review. The results of the studies (5 studies) which recruited patients with neurological conditions (most commonly MS) were largely in line with the overall trends identified by the Cochrane review. These studies comprised approximately 400 patients in total and were considered to be low-moderate quality evidence. The studies demonstrated modest but clinically relevant improvements in patients neuropathic pain symptoms. [2]

Evidence since the Cochrane Review

Systemic review M McDonagh et al 2022 [5]

The review carried out by McDonagh et al assessed cannabis-based products for chronic pain. The authors summarised that 56% of patient enrolled in the included studies had forms of neuropathic pain. The majority of studies included in this review were assessed as part of the Cochrane Review (some were excluded from the Cochrane review as part of this assessment). Three RCTs were included in this review which were not published when the Cochrane Review was being conducted.

Eighteen randomized, placebo-controlled trials (n= 1740) and 7 cohort studies (n= 13 095) assessed cannabinoids. Synthetic products with high THC-to-CBD ratios (>98% THC) may be

associated with moderate improvement in pain severity and response (≥30% improvement) and an increased risk for sedation and are probably associated with a large increased risk for dizziness. Extracted products with high THC-to-CBD ratios (range, 3:1 to 47:1) may be associated with large increased risk for study withdrawal due to adverse events and dizziness. Sublingual spray with comparable THC-to-CBD ratio (1.1:1) probably is associated with small improvement in pain severity and overall function and may be associated with large increased risk for dizziness and sedation and moderate increased risk for nausea. Evidence for other products and outcomes, including longer-term harms, were not reported or were insufficient.

The authors concluded that oral, synthetic cannabis products with high THC-to-CBD ratios and sublingual, extracted cannabis products with comparable THC-to-CBD ratios may be associated with short-term improvements in chronic pain and increased risk for dizziness and sedation. Studies are needed on long-term outcomes and further evaluation of product formulation effects.

Other efficacy data:

CADTH Review 2019 [5]

A Canadian review of efficacy and safety of medical cannabis for chronic pain has been used to inform this review. The review carried out by The Canadian Agency for Drugs and Technologies in Health (CADTH) provides Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in the Canadian health care system.

The CADTH report relied upon evidence from four overviews to draw its conclusions of clinical effectiveness. The review concluded that there is some suggestion of benefit with cannabis-based medicines for neuropathic pain. However, benefits need to be weighed against harms. Findings are inconsistent for the effect of cannabis-based medicines in patients with rheumatic disease, fibromyalgia, musculoskeletal pain, Crohn's disease, and MS.

The CADTH report also identified one systematic review of guidelines and four guidelines relating to cannabinoid use in neuropathic pain. The systematic review of guidelines recommends the use of cannabinoids as fourth-line treatment of neuropathic pain. [7] The guideline by Hauser et al. mentions that cannabis-based medicines can be considered as third-line therapy for chronic neuropathic pain. [8] The guideline by Allan et al. recommends against the use of medical cannabinoids for first- and second-line therapy for neuropathic pain (strong recommendation). It also mentions that under certain circumstances, medical cannabis could be considered for patients with refractory neuropathic pain (weak recommendation). [9] The College of Family Physicians of Canada (CFPC) guideline mentions that, before authorizing dried cannabis for treating neuropathic pain the physician should first adequately try other pharmacologic and non-pharmacologic therapies, followed by pharmaceutical cannabinoids. [10] The guideline by Moulin et al. recommends cannabinoids for the management of neuropathic pain but cautions that judicious prescribing practices are required. [11]

Meta-analysis A Bilbao [6]

This meta-analysis reviewed medical cannabinoids use in multiple indications including chronic pain (of which a number of included studies enrolled patients with neuropathic pain). The meta-analysis found that THC: CBD spray was associated with significant improvements and moderate evidence in conditions causing chronic pain.

British Pain Society Position Statement [13]

The British Pain Society have a produced a position statement which endorses NICE guidance NG 144 recommending that cannabis-based medicinal products should not be routinely prescribed for managing chronic pain. The British Pain Society summarises its positions as

follows:

- The British Pain Society will actively support the recommendations for further high-quality research into cannabis-based medicines.
- The British Pain Society supports the use of registries and databases in order to monitor people and assess who are most likely to benefit from medicinal cannabis and to safeguard patients against potential harm.
- The British Pain Society recommends that patients who have demonstrated objective benefit from medicinal cannabis following participation in a clinical trial, should have access to medical cannabis in the longer term with consideration of the burden of ongoing cost and medical supervision.
- The British Pain Society proposes that those existing patients with pain who have reported benefit from the use of recreational or illicit cannabis in the community for their chronic pain are carefully assessed for suitability for entry into clinical studies involving the therapeutic use of cannabis-based medicinal products.

Retrospective Cohort Study conducted at Lancashire Teaching Hospitals [14]

This is an unpublished audit/retrospective cohort study carried out at Lancashire Teaching Hospital. A patient cohort of 245 patients were selected based on having received a prescription for Sativex from the neurorehabilitation specialist at Preston during 2020-2021. The cohort included both MS (n=154) and non-MS (n=91) patients who had:

- continued with legacy prescriptions for the relief of both spasticity and refractory neuropathic pain
- recently been prescribed Sativex during this period, for the relief of refractory spasticity only, in accordance with NICE NG144 published in 2019.

Analysis of patient records (letters following appointments) indicates that following initiation of THC: CBD oromucosal spray, 33% of patients experienced improvements in their neuropathic pain symptoms. This was a higher proportion of patients than those expressing improvements in spasticity symptoms (21%).

Summary of safety data:

Safety data for the licensed use of Sativex

Adverse events

The 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. [1]

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. [1]

Contraindications

Sativex® is contraindicated in patients:

- With hypersensitivity to cannabinoids or to any of the excipients.
- 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.
- Who are breast feeding (in view of the considerable levels of cannabinoids likely in

maternal breast milk and the potential adverse developmental effects in infants).

Cautions

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.

There are no studies in patients with impaired renal function. However, in these sub-populations the effects of Sativex® may be exaggerated or prolonged. Frequent clinical evaluation by a clinician is recommended in these patient populations.

Use of Sativex® is not recommended in patients with serious cardiovascular disease. There is a risk of an increase in incidence of falls in patients whose spasticity has been reduced and whose muscle strength is insufficient to maintain posture or gait. In addition to an increased risk of falls, the CNS adverse reactions of Sativex®, particularly in elderly patients, could potentially have an impact on various aspects of personal safety, such as with food and hot drink preparation.

Although there is a theoretical risk that there may be an additive effect with muscle-relaxing agents such as baclofen and benzodiazepines, thereby increasing the risk of falls, this has not been seen in clinical trials with Sativex. However, patients should be warned of this possibility.

Adverse events in the relevant cohort

A Cochrane Review described the most commonly reported adverse events in patients with chronic neuropathic pain using cannabis-based. More people reported sleepiness, dizziness and mental problems (e.g. confusion) with all cannabis-based medicines pooled together than with placebo (low-quality evidence). There was moderate-quality evidence that more people dropped out due to side effects with cannabis-based medicines than with placebo. [2]

Strengths and limitations of the evidence:

Strengths

- There is a small group of patients with refractory chronic neuropathic pain and neurological conditions who have been unresponsive to four or more medicines or have been unable to gain adequate relief from non-pharmacological treatments.
- A Cochrane Review found there was low/moderate quality evidence demonstrating the effectiveness of cannabis-based medicines in the treatment of chronic neuropathic pain.
- A report produced for the Canadian health service concluded that the evidence suggests some benefit for medicinal-cannabis in the management of chronic neuropathic pain.
- The Canadian report also noted consensus guidelines advocating the use of medicinal-cannabis at specific points in the treatment pathway for chronic neuropathic pain.
- Sativex® has been licensed for the treatment of spasticity in MS for over 10 years. No major safety signals have been identified during this time.
- An audit of practice in a local trust which is responsible for the majority of Sativex® prescribing indicated that improvements in neuropathic pain symptoms were more commonly reported than improvements in any other symptoms.

Limitations

- The Cochrane review failed to find any high-quality evidence for the effectiveness of medicinal-cannabis for the management of chronic neuropathic pain. This may stem from the difficulties in conducting clinical trials in disabled patients with rare conditions.
- The doses of Sativex® required to provide adequate benefit to patients with refractory neuropathic pain may be significantly higher than the dose used in the licensed indication.
- The use of Sativex® for the management of chronic neuropathic pain is unlicensed and there is a lack of consensus guidance in the UK.

- Sativex® is significantly more expensive that the alternative pharmacological treatments for the management of refractory neuropathic pain.

Summary of evidence on cost effectiveness:

N/A

Prescribing and risk management issues:

For its licensed use, the SPC recommends that Sativex® treatment must be initiated and supervised by a physician with specialist expertise in treating this patient population. The SPC also recommends that the value of long-term treatment should be re-evaluated periodically.

Commissioning considerations:

Innovation, need and equity implications of the intervention:

There is experience of patients with refractory chronic neuropathic pain who have been unresponsive to two or more medicines or have been unable to gain adequate relief from non-pharmacological treatments.

Financial implications of the intervention:

According to an audit of prescribing by a local hospital trust there 245 patients were supplied with Sativex over the period of 2020-2021. According to the audit data 1% of patients (2 patients) were treated for refractory neuropathic pain (historic use prior to NICE recommendations).

Previously the LSCMMG estimated that less than 50 patients would be eligible for nortriptyline as a third line treatment for refractory neuropathic pain. Assuming that 20% of these patients did not respond to nortriptyline, it is estimated that less than 10 patients would be considered for Sativex treatment.

To treat 10 patients with Sativex using the dose ranges stated earlier in the review (i.e. 7 sprays daily in local practice compared to 48 sprays daily used in neuropathic pain in some clinical trials) would cost 10 X £2,838 to £19,464 = **£28,385 to £194,640**

Service Impact Issues Identified:

If made available, Sativex would be offered to a small number of patients with refractory neuropathic pain who are already in contact with specialist services due to the refractory nature of their symptoms. Therefore, there is not expected to be significant service impact issues.

Equality and Inclusion Issues Identified:

An equality assessment is included with the paper which is to be discussed at the meeting of the LSCMMG.

Cross Border Issues Identified:

Pan Mersey APC have an Amber “patient retained by specialist” RAG for Sativex® use in the licensed indication (treatment of refractory spasticity in MS). This allows prescribing in primary care following specialist recommendation. The patient is not discharged from specialist care. GMMMG have a Red RAG position for Sativex® in its licensed indication. Prescribing responsibility therefore remains with the specialist.
Legal Issues Identified:
N/A
Media/ Public Interest:
N/A

References

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[13] The British Pain Society, "The British Pain Society position statement on the use of medicinal cannabis and cannabis-based products in the management of chronic pain," October 2018. [Online]. Available: https://www.britishpainsociety.org/static/uploads/resources/files/BPS_position_statement_25_11_19.pdf. [Accessed September 2022].

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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