Shared Care Protocol
Sativex® for spasticity in Multiple Sclerosis

This shared care protocol (SCP) sets out details for the sharing of care for ***patients prescribed Sativex® in the management of spasticity in Multiple Sclerosis***

It should be read in conjunction with the latest Summary of Products Characteristics (SmPC) available at http://www.medicines.org.uk/emc/

As outlined in NHS England Guidance 2018 (07573), 'Responsibility for Prescribing Between Primary & Secondary/Tertiary Care': When a specialist considers a patient's condition to be stable or predictable, they may seek the agreement of the GP concerned (and the patient) to share their care.

This document provides information on drug treatment for the shared commitment between the specialist and GP concerned. GPs are invited to participate. If the GP is not confident to undertake these roles, then they are under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. The doctor who prescribes the medication has the clinical responsibility for the drug and the consequences of its use.

N.B. If the GP decides not to participate in shared care for a particular patient, they must inform the relevant specialist in writing, within 2 weeks of receipt of a request to share care.

For further information please click on the links below or visit:

- Sativex Oromucosal Spray - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)
- Overview | Cannabis-based medicinal products | Guidance | NICE
- Cannabis extract | Drugs | BNF | NICE

Introduction

Sativex® Oromucosal Spray 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.

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

Sativex is used in addition to a patient's current anti-spasticity medication.

This Shared Care Protocol is for adult patients aged 18 years and over.

NICE NG144 section 1.5.2 states:

After the initial prescription, subsequent prescriptions of cannabis-based medicinal products may be issued by another prescriber as part of a shared care agreement under the direction of the initiating specialist prescriber, if:

- shared care is appropriate and in the person's best interest
- the person's clinical condition is stable
- the other prescriber is confident to make a fully informed prescribing decision about cannabis-based medicinal products.

Licensed indication:

Sativex® Oromucosal Spray 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.

Each single 100 microlitre spray contains:
2.7 mg Delta-9-tetrahydrocannabinol (THC) and 2.5mg Cannabidiol (CBD)
from Cannabis sativa L.

Dose (posology & method of administration):

- Sativex is for oromucosal use only.
- 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.
- 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 (see 'Drug interactions').

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.

For full details see SmPCs at http://www.medicines.org.uk/emc/

Contra-indications:

- Hypersensitivity to cannabinoids or to any of the excipients.
- 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.
- Breast feeding (in view of the considerable levels of cannabinoids likely in maternal breast milk and the potential adverse developmental effects in infants).
- Pregnancy - The manufacturer states that **men and women** of childbearing potential should take reliable contraceptive precautions for the duration of therapy and for three months after discontinuation of therapy.

For full details see individual SmPCs at http://www.medicines.org.uk/emc/

Special warnings and precautions:

Cautions
History of epilepsy; significant cardiovascular disease

Hepatic impairment
Manufacturer advises avoid in moderate to severe impairment (risk of accumulation with chronic dosing)—no information available.

Renal impairment
Manufacturer advises more frequent monitoring in significant impairment (no information available; possible risk of prolonged or enhanced effect).

Other precautions & information

- Psychiatric symptoms such as anxiety, illusions, changes in mood, and paranoid ideas have been reported during treatment with Sativex.
- Disorientation (or confusion), hallucinations and delusional beliefs or transient psychotic reactions have also been reported and in a few cases a causal association between Sativex administration and suicidal ideation could not be ruled out.
- Increased risk of falls
- Patients who have a history of substance abuse, may be more prone to abuse Sativex as well.
- Patients should be advised that if they travel to another country, it may not be legal for them to take this medicine into some countries. They should be encouraged to check the legal status before travelling with Sativex.

The abrupt withdrawal of long-term Sativex treatment has not resulted in a consistent pattern or time-profile of withdrawal-type symptoms and the likely consequence will be limited to transient disturbances of sleep, emotion or appetite in some patients. No increase in daily dosage has been observed in long-term use, and patient self-reported levels of 'intoxication' are low. For these reasons, dependence on Sativex is unlikely.

Each actuation contains up to 40 mg of ethanol and 52 mg propylene glycol.

Effects on ability to drive and use machines
Sativex may produce undesirable effects such as dizziness and somnolence which may impair judgement and performance of skilled tasks. Patients should not drive, operate machinery or engage in any hazardous activity if they are experiencing any significant CNS effects such as dizziness or somnolence. Patients should be aware that Sativex has been known to cause a few cases of loss of consciousness.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988.
When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- **It is an offence to drive while under the influence** of this medicine

However, an offence might not be committed (called 'statutory defence') if:

- The medicine has been prescribed to treat a medical problem and
- It was taken according to the instructions given by the prescriber and in the information provided with the medicine and
- It was not affecting the ability to drive safely

For full details see SmPCs at http://www.medicines.org.uk/emc/

Fertility, pregnancy and lactation:

The manufacturer states that **men and women** of child bearing potential should take reliable contraceptive precautions for the duration of therapy and for three months after discontinuation of therapy.

Sativex may reduce the effectiveness of systemically acting hormonal contraceptives therefore, patients on hormonal contraceptives should be advised to use an additional alternative, non-hormonal/reliable barrier method of birth control during Sativex therapy.

Sativex is contraindicated in breastfeeding - it is excreted in milk.

Adverse effects & management:

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.

The list of reported side-effects is as follows:

Common or very common
Appetite abnormal; balance impaired; concentration impaired; constipation; depression; diarrhoea; disorientation; dizziness; drowsiness; dry mouth; dysarthria; euphoric mood; feeling drunk; malaise; memory loss; nausea; oral disorders; perception altered; taste altered; vertigo; vision blurred; vomiting

Uncommon
Abdominal pain upper; delusions; hallucinations; hypertension; palpitations; paranoia; pharyngitis; suicidal ideation; syncope; tachycardia; throat irritation; tooth discolouration

Adverse effect	Action to be taken by GP
Lesions or persistent soreness of oral mucosa	Interrupt treatment. Seek specialist advice if needed.

For full details see SmPCs at http://www.medicines.org.uk/emc/

Any adverse reactions should be reported to the MHRA via the Yellow Card scheme www.mhra.gov.uk/yellowcard

Drug interactions:

Potential for Sativex to affect other drugs/medicines:
Clinical doses of Sativex, could be sufficient to cause induction of CYP1A2, 2B6 and CYP3A4 at the mRNA level. Co-administration of Sativex may accelerate the metabolism and reduce the activity of these other drugs such as coumarins, statins, beta-blockers and corticosteroids.

Potential for Sativex to be affected by other drugs/medicines:
The two main components of Sativex, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are metabolised by the cytochrome P-450 enzyme system.

Cytochrome P-450 enzyme inhibition
Concomitant treatment with ketoconazole produced an increase in concentration of THC and of CBD. If concomitant drug treatment with CYP3A4 inhibitors (e.g. itraconazole, ritonavir, clarithromycin) is started or stopped during treatment with Sativex, a new dose titration may be required.
Concomitant treatment of Sativex (4 sprays) with fluconazole (200 mg capsule) resulted in an increase in mean THC, CBD and their active metabolites. Precaution should be taken when co-administering Sativex with potent CYP2C9 inhibitors.

Cytochrome P-450 enzyme induction
Following treatment with rifampicin reductions in THC, CBD and metabolite levels were observed. Therefore, concomitant treatment with strong enzyme inducers (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort) should be avoided whenever possible. If deemed necessary, careful titration is recommended, notably within the two weeks following the stop of the inducer.

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 may reduce the effectiveness of systemically acting hormonal contraceptives, and therefore women using systemically acting hormonal contraceptives should add an additional second barrier method.

This list is not exhaustive. The manufacturer's summary of product characteristics (SmPC) and the most current edition of the British National Formulary should be consulted for full information on contra-indications, warnings, side-effects and drug interactions.

Shared Care Responsibilities

Consultant responsibilities:

- Initial assessment of patient to determine eligibility for treatment, ensuring there are no interactions with concurrent therapy or disease states.
- A thorough evaluation of the severity of spasticity related symptoms and of the response to standard anti-spasticity medication should be performed prior to initiation of treatment.
- Counsel the patient about the benefits and risks of treatment and provide the patient with any relevant information and advice, including a patient information leaflet.
- Counsel the patient on the need to take reliable contraceptive precautions for the duration of therapy and for three months after discontinuation of therapy, if of childbearing potential (**men & women**). 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.
- To **prescribe the initial 4 week trial of Sativex** therapy, ensuring patient/carer has a basic understanding of what the drug is, how and when it should be taken why it is being used, and an awareness of potential side effects.
- Ensure the patient knows what significant adverse effects/events to report urgently and to whom they should report (specialist or GP).
- Notify the patient's GP that Sativex has been initiated and report progress following each clinic review, including if treatment is stopped.
- To **assess response to the initial 4 week** trial using a 0-10 spasticity numerical rating scale.
- If there is a clinically significant improvement (at least a 20% improvement in spasticity-related symptoms after the 4 weeks initiation period) without major tolerability issues then to **prescribe a further 2 months** of Sativex therapy.
- If a clinically significant improvement in spasticity related symptoms is not seen during this initial trial of therapy, then treatment should be stopped.
- Once the specialist considers the patient's medication regime to be stable, on a well-tolerated dose effective for symptom control, a request can be made to the patient's GP to 'share' the patient's care.
- The patient/carer should be informed of arrangements for further prescriptions.
- Any dose changes once the patient is established on treatment will be conveyed in writing to the GP for the GP to prescribe.
- The specialist will monitor response to treatment and side effects of medication on **annual follow-up consultation**. The value of long-term treatment should be re-evaluated periodically.

- All patients will remain under the ongoing care of a consultant neurologist or neurorehabilitation consultant.
- The consultant will provide support if problems occur using the contact details provided.
- The consultant will give directions as to when treatment should be discontinued.
- The consultant will provide the patient with written information about the treatment.

General Practitioner responsibilities:

- Accept request to take on prescribing of Sativex once the consultant considers the patient is stabilised on a tolerated dose effective for symptom control, no sooner than three months after initiation.
- At each appointment ensure that the patient/carer is clear what is being monitored and by whom:
    - GP – monitor side-effects and adherence
    - Specialist – monitor effectiveness
- Repeat prescribing of Sativex no sooner than three months after initiation, and once stable.
- Remind patient of the need to take reliable contraceptive precautions for the duration of therapy and for three months after discontinuation of therapy, if of childbearing potential (**men & women**). 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.
- Check drug interactions when any new medication started or any new condition diagnosed. Contact Specialist Team if possible interaction(s) found and discuss with Specialist.
- Amend prescription as per requests from specialist for dose changes in patients on established treatment.
- Seek Specialist advice promptly if signs/ symptoms or changes occur consistent with an adverse reaction.
- Stop treatment on advice of Specialist, or immediately if intolerable side effects occur, provided that it is safer to do so than to continue.
- Inform the specialist of any changes in the patient's medical condition and/or prescribed medication.
- Contact the specialist for support and advice as appropriate.

Patient / carer responsibilities:

- After counselling, to be willing to take / administer prescribed medication as directed at home.
- To report any significant signs or symptoms relating to their condition, including side effects or concordance issues to the specialist or GP.
- To take reliable contraceptive precautions for the duration of therapy and for three months after discontinuation of therapy, if of childbearing potential (**men & women**).
- To inform the specialist or GP immediately should pregnancy occur.

Specialist support

Name: Dr Simon Shields
Role and specialty: Consultant Neurologist, Head of Clinical Services
Daytime telephone number: 01823 342137
Email address: neurologyadmin@somersetft.nhs.uk
Alternative contact: Mrs. Marie Kelly; Specialist MS Nurse
Weekday contact duty neurologist details: via consultant connect service

Further support

• Medicines Information department, Musgrove Park Hospital: 01823 342253
• Medicines Information department, Yeovil District Hospital: 01935 384327
• Prescribing & Medicines Management Team, NHS Somerset: 01935 384123
• Medicines Management Team, Somerset NHS Foundation Trust: 01823 368265

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Version 1.1 updated by:	Hels Bennett, Medicines Manager, NHS Somerset ICB – Highlighted need for contraception in both **men & women** as per MPB	22.03.2023
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	Drug & Therapeutics Committee, Somerset NHS FT	
	MH Drug & Therapeutics Committee, Somerset NHS FT	N/A
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References

- Sativex Oromucosal Spray - Summary of Product Characteristics (SmPC) https://www.medicines.org.uk/emc/product/602/smpc#gref
- NICE Guideline NG144: Cannabis-based medicinal products - Published: 11 November 2019 Last updated: 22 March 2021 https://www.nice.org.uk/guidance/ng144
- https://bnf.nice.org.uk/drugs/cannabis-extract/