NHS Greater Glasgow and Clyde

CLINICAL GUIDELINE

Sativex® (use of) in Spasticity due to Multiple Sclerosis, Neuro Rehabilitation Unit (NRU)

A guideline is intended to assist healthcare professionals in the choice of disease-specific treatments.

Clinical judgement should be exercised on the applicability of any guideline, influenced by individual patient characteristics. Clinicians should be mindful of the potential for harmful polypharmacy and increased susceptibility to adverse drug reactions in patients with multiple morbidities or frailty.

If, after discussion with the patient or carer, there are good reasons for not following a guideline, it is good practice to record these and communicate them to others involved in the care of the patient.

Version Number:	1
Does this version include changes to clinical advice:	N/A
Date Approved:	28th April 2023
Date of Next Review:	28th February 2025
Lead Author:	Teng Cheng Khoo
Approval Group:	Regional Services Clinical Governance Group

Important Note:

The Intranet version of this document is the only version that is maintained.
Any printed copies should therefore be viewed as 'Uncontrolled' and as such, may not necessarily contain the latest updates and amendments.

NHS Greater Glasgow and Clyde	**NHS Greater Glasgow and Clyde** **Institute of Neurological Sciences & Neurorehabilitation Unit (NRU)** **Protocol for use of Sativex® in Spasticity due to Multiple Sclerosis**
Background:	Sativex® is licensed 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. Sativex® has been **accepted** for use within NHS Scotland by the Scottish Medicines Consortium in September 2022 and is now on the GGC formulary following local approval by the Area Drug and Therapeutics Committee. However, Sativex® should only be offered once other anti-spasticity medications have been considered and trialled appropriately. The purpose of this protocol is to establish criteria whereby Sativex® is offered to patients with MS. For patients with non-MS diagnoses being considered for Sativex®, as this will be an unlicensed use of the medication, this should be requested through the local Unlicensed Medication (ULM) process.
Agent and route[1]:	Sativex®, also known as nabiximols, is a specific Cannabis extract delivered as an oromucosal spray. Each single100 microlitre spray contains 2.7 mg delta-9-tetrahydrocannabinol (THC) and 2.5 mg cannabidiol (CBD) from Cannabis sativa L.
Licensed status:	Sativex® is licenced as treatment for symptom improvement in adult patients with moderate to severe spasticity due to 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]. Sativex® is classed as a schedule 4 Part I drug under the Misuse of Drugs Regulations 2001 and is subject minimal control, although records in a register must be kept.
Storage requirements:	Store in a refrigerator.
Indication and place in therapy:	Sativex® is indicated in the management of spasticity in patients with MS who have failed to demonstrate adequate response to first-line oral anti-spasticity medications. This applies to any spasticity-related symptoms, typically but not limiting to hypertonia, spasms and/or pain associated with spasticity. Figure 1 illustrates the management strategy for adult patients with MS presenting with spasticity and is adapted from the 2018 Royal College Physicians guidelines on "Spasticity in adults: management using botulinum toxin"[2]. This is strictly not a stepwise approach but involves a patient-centred goal-focussed assessment of potential treatment outcomes. In other words, Sativex® is not strictly limited in the management of generalised spasticity, and is usually used in conjunction with other treatment modalities in the attempt to achieve an intended treatment goal (e.g. passive goals such as reducing spasms/pain or facilitating moving and handling tasks, or active goals such as improving the consistency of physical transfers).

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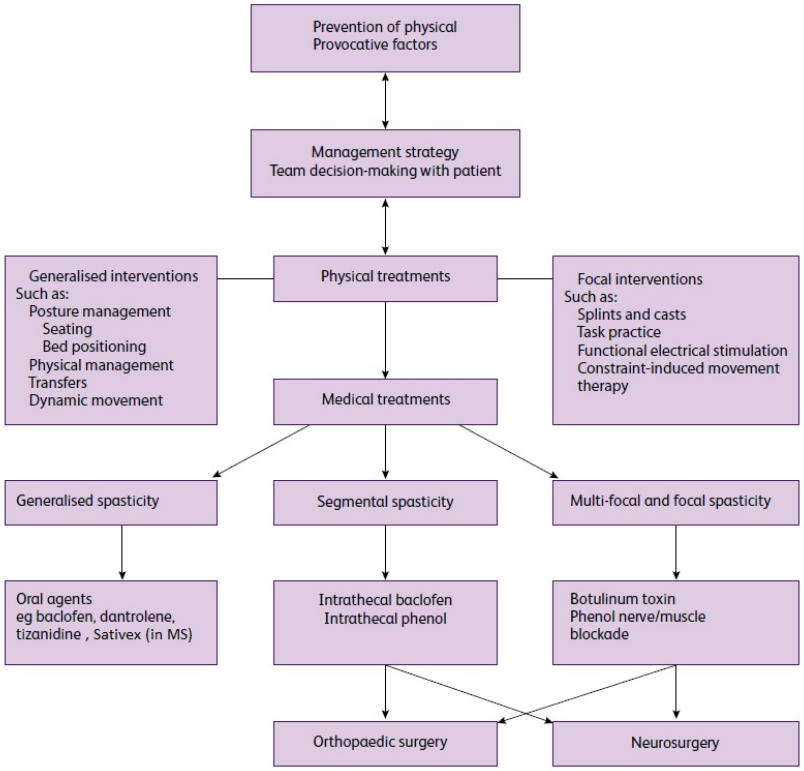
<tr><td></td><td> 

Figure 1. Management strategy for adults with spasticity (adapted from 2018 RCP guidelines).</td></tr>
<tr><td>Contraindications[1]:</td><td>Sativex® is contraindicated in patients:

• With hypersensitivity to cannabinoids.
• 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).</td></tr>
<tr><td>Adverse effects[1]:</td><td>The most commonly reported adverse reactions in the first four weeks of use are 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. The incidence of dizziness and fatigue in the first four weeks is minimised by following the dose titration schedule recommended in the SPC. 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.

Patients may also experience discomfort in the mouth, but this can be eased by varying the area of the mouth to which Sativex® is applied.

Psychiatric symptoms such as anxiety, confusion or disorientation, illusions or hallucinations, changes in mood, changes in mood and paranoid ideas have been reported during treatment with Sativex®. These should remit on interruption of treatment and be minimised thereafter by careful dose reduction.</td></tr>
<tr><td>Drug Interactions[1]:</td><td>• Hypnotics – sedatives and drugs with potential sedating effects – possible additive effect on sedation.
• Amitriptyline – plasma levels may be increased, but no evidence of interaction at doses of 75 mg or less daily.</td></tr>
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The effects of alcohol may be potentiated affecting co-ordination, concentration and ability to respond quickly.
Both active components are cleared by liver enzymes, there are a range of drugs which can increase and also decrease this clearance, please check for potential interactions when introducing further therapy once the patient is stabilised on Sativex®.

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<tr><td>Trial process:</td><td>
As per relevant NICE guidelines, a 4 week trial of Sativex® should be considered in adult patients with MS with moderate to severe spasticity if they have failed to demonstrate an adequate response (or adverse effects) with at least 3 anti-spasticity medications. This must include Baclofen, Tizanidine and Gabapentin/Pregabalin at maximum tolerated doses. After the 4-week trial, Sativex® can be continued if the person has had at least a 20% reduction in spasticity-related symptoms on a 0 to 10 patient-reported numeric rating scale (NRS)[3-4]. Otherwise, this should be discontinued.

Treatment with Sativex® should be initiated and supervised by a physician with specialist expertise in treating spasticity due to MS, in line with its marketing authorisation. At present, NRU conducts the Sativex® trials and ongoing monitoring for patients with MS, but the trial of first-line medications (i.e. Baclofen, Tizanidine and Gabapentin/Pregabalin) should not be limited to clinicians at NRU. If a specific referral to NRU is made to consider Sativex®, the referrer (e.g. Neurologist, MS nurse specialist) should make sure that the first-line anti-spasticity medications have been adequately trialled where appropriate.

At NRU, once a patient with MS is deemed appropriate to trial Sativex® at clinic, a pre-trial checklist should be completed (Appendix 1), before a prescription is organised. Baseline NRS in spasticity, spasms and pain are collected as the minimum outcome measure dataset. A Patient Information Leaflet outlining the titration schedule (see below) is also handed out. A follow-up telephone appointment is organised at 4 weeks where a post-trial checklist is completed (Appendix 2).

An extended trial for a further 4 weeks may be organised in certain circumstances (e.g. intercurrent illness impacting on spasticity symptoms during initial trial) before a final judgement is made in relation to the effectiveness of Sativex®.
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<tr><td>Dose, duration and administration:</td><td>
The ideal dose varies from person to person but may be about 8 sprays per day. It is recommended that the dose is titrated over the initial two weeks of starting treatment and reviewed at 4 weeks as per the trial process.

<u>Titration period</u>:

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 symptomatic relief. There should be at least a 15 minute gap between sprays.

<table>
<tr><th>Day</th><th>Number of sprays in the morning</th><th>Number of sprays in the evening</th><th>(Total number of sprays per day)</th></tr>
<tr><td>1</td><td>0</td><td>1</td><td>1</td></tr>
<tr><td>2</td><td>0</td><td>1</td><td>1</td></tr>
<tr><td>3</td><td>0</td><td>2</td><td>2</td></tr>
<tr><td>4</td><td>0</td><td>2</td><td>2</td></tr>
<tr><td>5</td><td>1</td><td>2</td><td>3</td></tr>
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Prescription and monitoring:	When a patient with MS has had a successful Sativex® trial, a request for the GP to take over the prescription will be made, with the responsibility of ongoing monitoring of the use of Sativex® remaining with NRU. There is currently no Shared Care Agreement in place for Sativex®. If declined by GP, the prescription will continued to be organised by NRU. In terms of frequency of monitoring, this is set initially at 6 months and will be conducted as a telephone review. During monitoring appointments, the relevant outcome measures for the patient are revisited, along with the Sativex® dosage and tolerability. If things remain stable for a year, the monitoring interval will be increased to yearly appointments. These monitoring appointments are organised separate from any ongoing NRU outpatient appointments for the patient.
References:	1. Sativex® oromucosal Spray Summary of Product Characteristics (last updated on eMC 24 Aug 2018). Available from https://www.medicines.org.uk/emc/product/602 2. RCP Guideline: Spasticity in adults management using botulinum toxin, 2018. Available from: http://www.rcplondon.ac.uk/guidelines-policy/spasticity-adults-management-using-botulinum-toxin 3. NICE Clinical Guideline 144: Cannabis-based medicinal products, November 2019. Available from: https://www.nice.org.uk/guidance/ng144 4. NICE Clinical Guideline 220: Multiple sclerosis in adults: management, June 2022. Available from: http://https://www.nice.org.uk/guidance/ng220
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Date prepared:	February 2023
Review Date:	February 2025

Appendix 1

Sativex Pre-Trial Checklist

[attach patient label]

NHS Greater Glasgow and Clyde

This checklist is intended for patients with Multiple Sclerosis only. This is not to be used for patients with other diagnoses trialing on Sativex. Please refer to NHSGGC Sativex Protocol for more details.

Clinical Details

Type of MS : ☐ RRMS ☐ SPMS ☐ PPMS

Year of Diagnosis :

Therapeutics trialed : ☐ Baclofen ☐ Gabapentin/Pregabalin ☐ Tizanidine

☐ Dantrolene ☐ Benzodiazepines ☐ Botulinum toxin

☐ Others:

Proceed only if have trialed at least Baclofen, Gabapentinoids and Tizanidine at maximum tolerated dose without benefit, and/or if felt not appropriate.

Contraindications to Sativex

- Hypersensitivity to cannabinoids. Yes / No
- 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. Yes / No
- Breastfeeding (in view of the considerable levels of cannabinoids likely in maternal breast milk and the potential adverse developmental effects in infants). Yes / No

Proceed only if answered "No" to the above.

Pre-Trial Baseline Measurements

Numerical Rating Scales (0-10):

Spasticity	Spasms	Pain

Other measures where relevant:

Other Checklist

☐ Patient information leaflet handed to patient/family.

☐ Sativex prescription arranged with NRU secretaries to be sent to Neuropharmacy.

☐ Email NRU secretaries to arrange post-trial telephone review (once patient picks up prescription).

Upload completed checklist to Clinical Portal.

Date of Consultation: Clinician Name and Signature:

Appendix 2

Sativex Post-Trial Checklist

[attach patient label]

This checklist is intended for patients with Multiple Sclerosis only. This is not to be used for patients with other diagnoses trialing on Sativex. Please refer to NHSGGC Sativex Protocol for more details.

Clinical Details

- Date started Sativex:
- Sativex tolerated: Yes / No

  If not tolerated, elaborate:
- Current number of sprays:

Post-Trial Baseline Measurements

Numerical Rating Scales (0-10):

Spasticity	Spasms	Pain

Other measures where relevant:

Trial Outcome

Successful Trial (≥20% improvement): YES / NO

Extended trial required?: Yes / No

If yes, elaborate:

Other Checklist

☐ Sativex trial outcome documentation to be dictated. If successful, include letter to GP to request take over of Sativex prescription, and medical letter for patient to explain use of Sativex.

☐ Follow-up surveillance review to be arranged.

Upload completed checklist to Clinical Portal.

Date of Consultation: Clinician Name and Signature: