DERBYSHIRE JOINT AREA PRESCRIBING COMMITTEE (JAPC)

Sativex® for moderate to severe spasticity in multiple sclerosis (MS)- prescribing guideline in primary care

Sativex® (cannabidiol 2.5mg + dronabinol 2.7mg per dose) oromucosal spray for the treatment of moderate to severe spasticity in multiple sclerosis in line with NICE NG 144 has been re-classified from RED to **Green after consultant/ specialist initiation**

Background

Cannabis-based medicinal products have been suggested for a variety of medical conditions. In line with prescribing for all medicines, the potential for harm must be weighed up against the potential for benefit for individual patients.

Sativex® is a UK licensed product containing delta-9-tetrahydrocannibinol (THC) combined with cannabidiol (CBD). NICE NG144 (November 2019) recommends

- Offer a **4-week trial** of THC:CBD spray [Sativex] to treat moderate to severe spasticity in adults with multiple sclerosis (MS), if:
  - **other pharmacological treatments for spasticity are not effective**, and
  - the company provides THC:CBD spray according to its pay-for-responders scheme
- After the 4-week trial, continue Sativex 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).
- Treatment with Sativex should be initiated and supervised by a physician with specialist expertise in treating spasticity due to multiple sclerosis, in line with its marketing authorisation.

Sativex is licensed by the MHRA as a treatment for symptom improvement of moderate to severe spasticity in adults with MS and recommended by NICE as an add-on treatment for adults with treatment resistant spasticity due to MS. Restrictions on prescribing of unlicensed medicines or 'specials' do not apply to Sativex in its licensed indication.

JAPC classified Sativex RED (specialist only) in line with NICE NG144 in June 2020 to allow clinician to gain experience of use in this cohort of patients. Following further discussion, Sativex has been re-classified Green after consultant/ specialist initiation to enable better patient access. However, the responsibility to review patient response remains with the specialist MS team.

Management of spasticity in MS

Pharmacological treatments:

- Ensure that each drug has been trialled at the optimal dose or to the maximum tolerate dose
- stop the drug if there is no benefit at the maximum tolerated dose (but adhere to any recommended precautions when stopping specific drugs)
- ensure that the drug treatment is reviewed at least annually once the optimal dosage has been reached.

1st line	Baclofen or Gabapentin
2nd line	Consider Baclofen and Gabapentin in combination, if individual drugs do not provide adequate relief **or** side effects from individual drugs prevent the dose being increased
3rd line	Tizanidine or Dantrolene
4th line	Benzodiazepines (be aware of their potential benefit in treating nocturnal spasms).

Patients must have had an adequate trial of at **four alternative** oral anti-spasticity treatments before considering treatment with Sativex.

Specialist responsibility

- To confirm that the patient is suitable for treatment with Sativex in line with NICE NG144 and the Sativex care pathway. Patients must have had an adequate trial of at **four alternative** oral anti-spasticity treatments.
- To confirm that the there are no contraindications to treatment initiation:
    - hypersensitivity to cannabinoids or any of the excipients contained in Sativex
    - history of severe mental health disorder, including psychotic illness
    - breastfeeding
- To **initiate, stabilise, and supply treatment of Sativex for the first 2 months** of treatment.
    - The specialist team will initially supply one month's treatment (3 x 10ml vials) and provide the patient with instructions as to how to prime the vial, administer spray and titrate the dose to the optimum amount (typically 4-8 sprays/day; max 12) over 2 weeks
    - During this first 2 weeks titration period the patient will be advised not to drive if experiencing side effects.
    - Once the optimum dose has been determined, treatment can be used at any time of the day or night depending on symptoms, but leaving at least a 15-minute gap between sprays
- To inform the patient of the importance of appropriate contraception.
    - Women of childbearing potential should avoid pregnancy and use a highly effective contraceptive for the duration of therapy and for 3 months after discontinuation.
    - Sativex may reduce the effectiveness of systemically acting hormonal contraceptives, necessitating the addition of a barrier contraceptive.
- To check for any interactions with Sativex and the patients existing medication
- To inform patients of practical issues related to the use of Sativex, such as storage and maximum dose.
- **To carry out baseline record of the Numeric Rating Scale (NRS), and to assess response 28 days after initiation. Only continue treatment with Sativex if at least 20% reduction in spasticity-related symptoms is achieved.**
- To consider asking GP to issue ongoing prescription if 20% reduction in spasticity-related symptoms is achieved and after initial 28 days and patient is on a stable dose.
- **To review patient 1 month post initiation, at 6 months (specialist- nurse led), 12months (consultant-led); and on an annual basis (consultant-led) thereafter.**
- To ensure that arrangements are in place for GPs to obtain advice and support where needed. To communicate promptly with the GP the results of any monitoring undertaken in secondary care and any changes to treatment made by the specialist.

Primary care responsibility

- Following specialist initiation, to provide ongoing prescriptions for Sativex after the first 2 months of treatment, for patients who have been found to benefit from treatment.
- To adjust the dose as advised by the specialist
- To report and seek specialist advice regarding any concerns, e.g.
    - side-effects (possible allergic reactions, excessive somnolence, dizziness)
    - co-morbidities where caution should be taken (seizures, severe cardiovascular disease, mental illness)
    - pregnancy
    - lack of efficacy
- To report concurrent use of illicit cannabis or other drugs of abuse to the MS specialist team (MS Specialist Nurse, Consultant, or Pharmacist).
- To monitor ongoing use of Sativex to ensure appropriate quantities are ordered and to contact the MS Specialist if there are any issues of concern. This includes if the patient requests excessive repeat prescriptions.
- To refer back to hospital specialist if condition deteriorates or if non-compliance expected.

Clinical information

For further detail refer to the Summary of Product Characteristics (SPC)

indications	Sativex oromucosal spray is indicated as treatment for symptom improvement in patients with **moderate to severe spasticity due to Multiple Sclerosis (MS)** who • have not responded to at least four anti-spasticity medications and • demonstrate clinically significant improvement in spasticity related symptoms (at least 20% reduction on NRS scale) during an initial trial of therapy
Dose	A titration period (up to 2 weeks, see SPC) is required to reach optimal dose. The number and timing of sprays will vary between individual patient (usually 4-8 sprays per day). Max. dose 12 sprays per day with a min.15 minutes between sprays **Prescribe in multiples of 10ml vials, in words and figures - schedule 2** 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. Starting or stopping some concomitant medicinal products may require a new dose titration.
Monitoring Requirements	**Consultant:** Baseline record of the Numeric Rating Scale (NRS) Assess response 28 days after initiation. Review patient at the request of GP / MS specialist nurse or pharmacist should any problems arise. **MS Specialist Nurse:** Monitor for efficacy, significant side-effects and overuse at 1 month, 3 months and 6 months. The patient will then continue with routine annual review with MS Specialist Nurse/MS clinic. **GP:** Report any concerns about side-effects (possible allergic reactions, excessive somnolence, dizziness), co-morbidities (seizures, severe cardiovascular disease, mental illness), pregnancy, overuse or lack of efficacy, concurrent use of illicit cannabis or other drugs of abuse to the MS specialist team (MS nurse, consultant or pharmacist). Routine blood monitoring is not required. All individuals involved on the patients care have responsibility to report any suspected adverse effects to the MHRA: http://www.yellowcard.gov.uk
Contra-indications	• Hypersensitivity to cannabinoids or to any of the excipients. • 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. • Women who are breast-feeding.
Pregnancy, paternal exposure and breastfeeding	**Pregnancy** Sativex should not be used during pregnancy unless the potential risks to the fetus and/or embryo are considered to be outweighed by the benefit of treatment. **Lactation** Available pharmacodynamics / toxicological data in animals have shown excretion of Sativex / metabolites in milk. A risk to the breastfed child cannot be excluded. Sativex is contraindicated during breast-feeding

Adverse effects	• The most reported side effects are dizziness and fatigue, which occur mainly during the initial titration period. • These reactions are usually mild to moderate and normally resolve within a few days even if treatment is continued. • 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. • Sativex does not typically cause a 'high' comparable with recreational cannabis use. • 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 could potentially have an impact on various aspects of personal safety, such as with food and hot drink preparation. • If side effects occur the dose should be lowered by 1-2 sprays/day, in the case of oral irritation the patient should be advised to vary the site of the spray around the mouth and avoid any ulcers or irritated areas.
Consider stopping treatment	• Lack of efficacy • Excessive adverse effects which are not tolerated • Pregnant/ planning to become pregnant or breastfeeding • Concurrent use of illicit cannabis or other drugs of abuse • Misuse of Sativex • Moderate/ severe hepatic impairment
Clinically relevant drug interactions	• There is a theoretical risk that there may be an additive effect with other muscle-relaxing agents such as baclofen and benzodiazepines, thereby increasing the risk of somnolence, weakness and falls. • Sativex is metabolised by the Cytochrome P-450 enzyme system, therefore enzyme inducers or inhibitors may decrease or increase the concentration of Sativex in the circulation. Seek specialist advice if necessary. • Sativex may reduce effectiveness of systemically acting hormonal contraceptives, therefore women using systemically acting hormonal contraception for example the oral contraceptive pill or contraceptive implant should use an additional second barrier method of contraception for the duration of therapy and for three months after discontinuation. • Care should be taken with hypnotics, sedatives and alcohol due to the additive side effects.
Supply, storage and reconstitution instructions	**Travel:** When travelling abroad patient will need to check with the Home Office if Sativex is legal in the country they are due to visit and they should request a letter from their MS specialist. **Storage:** It should be stored in the fridge but once opened it can be kept out of the fridge for up to 42 days. It should be kept upright.

Contact Detail

UHDB Consultant via switchboard:01332 340131
MS Specialist Nurse: 01332 783537
Neurology Department: 01332 786478

Further information/ resources

NHSE Cannabis-based products for medicinal use https://www.england.nhs.uk/medicines-2/support-for-prescribers/cannabis-based-products-for-medicinal-use/	Guidance to clinicians: The process for prescribing cannabis-based products for medicinal use Prescribing of THC:CBD spray (Sativex®) in line with NICE NG144 **Cannabis-based products for medicinal use: Frequently asked questions**
MS patient website	Sativex (nabiximols) | Multiple Sclerosis Society UK (mssociety.org.uk) Sativex (nabiximols) | MS Trust

Reference

NICE NG144 Cannabis-based medicinal products https://www.nice.org.uk/guidance/ng144 [accessed June 2022]

Medicinal use of cannabis-based products and cannabinoids. BMJ 2019;365:l1141 https://doi.org/10.1136/bmj.l1141 [accessed June 2022]

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