South Tyneside and Sunderland
Area Prescribing Committee

SHARED CARE GUIDELINE

Sativex for the treatment of spasticity in multiple sclerosis

Implementation Date: July 2020 **Review Date: July 2023**

This guidance has been prepared and approved for use within South Tyneside and Sunderland in consultation within the CCG, and Secondary Care Trusts.
The guideline sets out the details of the transfer of prescribing and respective responsibilities of GPs and specialist services within shared care prescribing arrangements. It is intended to provide sufficient information to allow GPs to prescribe this treatment within a shared care setting

Approved by:

Committee	Date
STS Area Prescribing Committee	**June 2020**

Instructions for completion:

- Consultant to counsel patient on medication and ensure patient has been provided with information leaflet
- Consultant to ensure all clinical details completed on this document
- Consultant to ensure patient understands proposed monitoring and prescribing arrangements if a shared care agreement is entered into
- GP to complete final section of form and return to specialist prescriber within 28 days
- GP to retain copy of document on patient record within surgery

Clinical details:

SHARED CARE GUIDELINE					
Non-proprietary name	Delta-9-tetrahydrocannabinol (THC) and Cannabidiol (CBD)	**Brand name**	Sativex	**Licensed Y/N?**	Yes
Dosage form and strength	Oromucosal spray, solution Each single 100 microlitre spray contains: 2.7 mg delta-9-tetrahydrocannabinol (THC) and 2.5 mg cannabidiol (CBD) from Cannabis sativa L.			**BNF class**	10.2.2
Indication	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. Sativex is intended to be used in addition to the patient's current anti-spasticity medication.				
Dosage and Administration	Treatment must be initiated and supervised by a physician with specialist expertise in treating MS. **Administration** Sativex is for oromucosal use only and must be shaken before use. The spray must 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. **Initiation** 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.				

	A titration period is required to reach an optimal dose. The number of sprays will be increased each day in the hospital initiation phase until the optimum dose for symptom relief is obtained. It may take up to 2 weeks to find the optimal dose and a response to treatment requires review in 4 weeks. On review by specialist, if there is no significant improvement in spasticity-related symptoms during initial trial of therapy, Sativex is stopped. A clinically significant improvement is defined as at least a 20% improvement in spasticity-related symptoms on a 0-10 patient reported numeric rating scale. The spray is firstly initiated in the evening, and all evening doses should be taken any time between 4pm and bedtime. When the morning dose is introduced, it should be taken 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. The number and timing of sprays will vary between patients. The number of sprays is increased according to the summary product of characteristics. The median dose in clinical trials for patients with MS was 8 sprays per day. In routine clinical practice, the median number of daily sprays used by MS patients was 4. **Maintenance** Patients are advised to maintain the optimum dose achieved. Once the optimum dose has been achieved, the patient may spread out the total dose across 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. Long term treatment will be re-evaluated periodically.
Eligibility criteria for shared care	Patients must: 1. Be under the care of a consultant neurologist or neurorehabilitation consultant. 2. Have a diagnosis consistent with indication above. 3. Have received Sativex for 4 weeks and reached a stable dose, that is well-tolerated. 4. Have had at least a 20% improvement in spasticity-related symptoms.
Excluded patients	Not for use in in children or adolescents under 18 years of age. Patients in whom Sativex is not tolerated or contraindicated.
Initiation	Shared care to be initiated once patient has been receiving Sativex for 4 weeks, a 20% improvement in spasticity related symptoms has been achieved and dose is stable and well tolerated.
Specialist Responsibilities	**Specialist to:** **Initiation** 1. Conduct baseline spasticity monitoring. 2. Review patient suitability (cautions/contraindications/ drug interactions) for Sativex in conjunction with patient/carer. 3. Counsel on indication, intended therapeutic benefit, administration and side effects 4. Advise patient that it might take up to 2 weeks to find the optimal dose and that undesirable effects can occur during this time, most commonly dizziness. These undesirable effects are usually mild and resolve in a few days. Specialist should consider maintaining the current dose, reducing the dose or interrupting, at least temporarily, the treatment depending on seriousness and intensity. 5. Provide written information regarding Sativex use and the titration schedule as per summary of product characteristics. 6. Provide and counsel patient on how to complete the NRS spasticity diary. 7. Prescribe first Sativex prescription using the 'Sativex FOC' entry on Meditec.

	8. Complete and send the 'Sativex pay for responder order form for NHS patients' provided by Bayer and send to Outpatient Pharmacy (Choice), in order for pharmacy to order FOC Sativex .Outpatient pharmacy to liaise with pharmacy stores for ordering FOC Sativex. 9. Post-titration, review if a 20 % reduction in muscle spasticity has been achieved via the completed NRS spasticity diary after 4 weeks of treatment. 10. If 20 % reduction in spasticity achieved and dose is stable and well tolerated, to complete shared care request/confirmation form. One copy to be sent to G.P and one copy to be scanned onto Medisec by secretary. 11. Prescribe 28 days supply of chargeable Sativex. **Maintenance** 12. Communicate any changes to future prescriptions with the patient and GP, usually within 24 hours. 13. Review the treatment yearly, during the annual review of the patient by member of MS team. 14. Provide advice to GP should there be any changes in the severity of the patient's condition, significantly interacting medication initiated/discontinued or if troublesome adverse reactions develop. 15. If SCG acceptance is not achieved, to continue to prescribe chargeable Sativex
GP Responsibilities	1. GP to provide monthly prescriptions. 2. GP to contact MS team if any significant side effects or concerns about efficacy. If significant psychiatric side effects (e.g. psychosis, suicidal thoughts), to *stop medication* and contact MS team immediately, as well as psychiatry, if required.

<table>
<tr><td>Precautions</td><td>Clinician should review severity of side effect and contact specialist for advice if needed, side effects outlined below:

• Sativex is not recommended for use in children or adolescents below 18 years of age .
• Elderly patients may be more prone to develop CNS adverse reactions; care should be taken in terms of personal safety when undertaking tasks such as preparation of hot food and drinks.
• No data is available for patients on a multiple dosing regimen who have hepatic impairment.
• Sativex can be administered to patients with mild hepatic impairment without any dose adjustment
• Administration to patients with moderate or severe hepatic impairment is not advised due to lack of information for the potential for accumulation of THC and CBD with chronic dosing.
• There are no studies in patients with impaired renal function. In these patient groups the effects of sativex may be exaggerated or prolonged and frequent monitoring by the clinician is recommended.
• Women of childbearing potential must use highly effective contraception whilst taking Sativex. The effects on hormonal contraception are unknown, therefore women should use an additional method of contraception both during and for 3 months after discontinuation.
• Use of Sativex is not recommended in patients with serious cardiovascular disease
• Until further information is available, caution should be taken when treating patients with a history of epilepsy, or recurrent seizures.
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<tr><td>Contraindications</td><td>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 psychiatric disorder other than depression associated with their underlying condition.
• Breastfeeding</td></tr>
<tr><td>Adverse Effects</td><td>
<table>
<tr><th></th><th>Very Common ≥ 1/10</th><th>Common ≥ 1/100 to < 1/10</th><th>Uncommon ≥ 1/1000 to < 1/100</th><th>Action required by GP</th></tr>
<tr><td>Infections and infestations</td><td></td><td></td><td>pharyngitis</td><td></td></tr>
<tr><td>Metabolism and nutrition disorders</td><td></td><td>anorexia (including appetite decreased), appetite increased</td><td></td><td></td></tr>
<tr><td>Psychiatric disorders</td><td></td><td>depression, disorientation, dissociation, euphoric mood,</td><td>hallucination (unspecified, auditory, visual), illusion, paranoia, suicidal ideation, delusional perception*</td><td>STOP drug, informs team and seek psychiatric advice if appropriate.</td></tr>
<tr><td>Nervous system disorders</td><td>dizziness</td><td>amnesia, balance disorder, disturbance in attention, dysarthria, dysgeusia, lethargy, memory impairment somnolence</td><td>syncope</td><td></td></tr>
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	Eye disorders		vision blurred		
	Ear and labyrinth disorders		vertigo		
	Cardiac disorders			palpitations, tachycardia	
	Vascular disorders			hypertension	
	Respiratory, thoracic and mediastinal disorders			throat irritation	
	Gastrointestinal disorders		constipation, diarrhoea, dry mouth, glossodynia, mouth ulceration, nausea, oral discomfort, oral pain, vomiting	abdominal pain (upper), oral mucosal discolouration*, oral mucosal disorder, oral mucosal exfoliation*, stomatitis, tooth discolouration	
	General disorders and administration site conditions	fatigue	application site pain, asthenia, feeling abnormal, feeling drunk, malaise	application site irritation	
	Injury, poisoning and procedural complaints		fall		

Common Drug Interactions

See manufacturers data sheet for more detail

<u>Potential for Sativex to affect other drugs/medicines</u>

CYP induction study suggest clinical doses of Sativex, could be sufficient to cause induction of CYP1A2, 2B6 and CYP3A4 at the mRNA level.

Co-administration of Sativex with drugs such as coumarins, statins, beta-blockers and corticosteroids may reduce efficacy and require dose adjustment.

<u>Potential for Sativex to be affected by other drugs/medicines</u>

The two main components of Sativex, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are metabolised by the cytochrome P-450 enzyme system.

<u>Cytochrome P-450 enzyme inhibition</u>

Concomitant treatment with Ketoconazole produced an increase in THC levels, its primary metabolite and CBD levels. Therefore, 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 the CYP2C9 inhibitor fluconazole (200 mg capsule) resulted in an increase in mean THC .Exposure to the metabolite 11-OH-THC also increased indicating fluconazole may inhibit its subsequent metabolism. The C_{max} of CBD also increased by approximately 40 % but there was no significant change in AUC.

The clinical relevance of this drug-drug interaction is not fully understood, however care should be taken when co-administering Sativex with potent CYP2C9 inhibitors as it may lead to an increase

	in exposure to THC, CBD and their metabolites. Cytochrome P-450 enzyme induction Following treatment with the CYP3A4 inducer rifampicin reductions in C_{max} and AUC of THC (40% and 20% reduction, respectively), its primary metabolite (85% and 87% reduction, respectively) and CBD (50% and 60% reduction, respectively) 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. UGT enzymes Sativex was found to inhibit the UGT enzymes UGT1A9 and UGT2B7 at concentrations that could be achieved in the clinic. Care should be taken when prescribing Sativex with concomitant medications which are solely metabolised by both or either of these UGTs (e.g. Propofol and certain antivirals). Patients with genetic glucuronidation disorders (e.g. Gilbert's disease) may exhibit increased serum concentrations of bilirubin and must be treated with caution when Sativex is co-administered. 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.
Communication/ Contact Details	*Victoria Jones – MS co-ordinator: 0191 5656256 Ext 5656256* *MS Specialist Nurse – Carmel Wilkinson: Working hours: Monday to Thursday 08.30-5pm* *Contact details Bleep : 52076 Secretary :Victoria Jones Telephone :0191 5656256 Ext:: 47152* *Consultant Kate Petheram: Working hours Monday to Wednesday. Secretary Sue Berry 0191 5656256 Ext: 42778* *Consultant Gemma Maxwell: Working hours Monday to Thursday. Secretary Cindy Morrow 0191 5656256 Ext: 42552*

This information is not inclusive of all prescribing information and potential adverse effects. Please

Shared Care Request/Confirmation .....Private and Confidential

Patient information:
To be completed by specialist prescriber:

Consultant ……	**Patient details (use hospital label if preferred)**
Department ……	**Name** ……
Hospital ……	**Address** ……
	……
	Postcode ..... **Sex** ……..
	NHS or Hosp. Reg. No. …… **DoB** ……..

Treatment Requested for Prescribing in Accordance with Shared Care Arrangement:
To be completed by specialist prescriber:

Drug name	
Dose	
Frequency	
Indication	
Other information	I confirm Sativex is clinically effective (20% reduction in spasticity) and is to continue on a stab dose. Last supply = 28 days supplied on ……

Name (print)…….. Signature (of specialist prescriber)……..…….. Date……..

Acceptance/rejection of treatment under Shared Care Agreement:
To be completed by GP:

Please tick one box

I ACCEPT the proposed shared care arrangement for this patient ❑

or

I ACCEPT the proposed shared care arrangement with the caveats below ❑

or

I DO NOT ACCEPT the proposed shared care arrangement for this patient ❑

My caveats / reason(s) for not accepting include: ……
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Name (print)…….…. Signature (of GP)……..……..... Date……

N.B. Participation in this shared care arrangement implies that prescribing responsibility is shared between the specialist prescriber and the patient's GP